

PRACTICAL VACCINE TREATMENT

FOR THE GENERAL PRACTITIONER

R. W. ALLEN



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FOR THE GENERAL PRACTITIONER

BY

R. W. ALLEN

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INTRODUCTION

He who knows not and knows not that he knows not is a child—
teach him;

He who knows not and knows that he knows not is a fool—shun
him;

He who knows and knows not that he knows is asleep—wake him;

He who knows and knows that he knows is a wise man—follow
him.

OLD PERSIAN PROVERB.

FOR many years my voice has been the voice of one crying in the wilderness; almost alone have I preached the doctrine of dosages capable of exciting a reaction, of dosages and intervals controlled by close clinical observation of the responses made by the patient's tissues to the impulses administered to them; I have repeatedly shown how these observations are to be made, and how they are to be interpreted and utilized for the benefit of the patient.

Arrayed against me have been the forces of those who, misled perhaps by a faulty and inadequate intelligence department, have feared to put forth their own full strength, to employ the ample therapeutic forces at their disposal, and to call upon their allies, the healthy tissues, for all the help they could afford. To-day these stand before the tribunal and have to answer for much of the discredit that has fallen to the share of their ill-marshalled and ill-led forces.

Not once, but again and yet again, incapable

apparently of learning from the disasters of the past, have they sent out platoons to do the work of battalions and even of army corps. In other words and to give a concrete example, almost every writer upon the subject of vaccine treatment in this country but myself will even now tell you to immunize a patient against a pneumococcal cold or bronchitis with a dose of 25-50 millions: for years I have employed autogenous doses of at least 500 millions for the purpose, and lately Avery, Chickering, Cole, and Dochez in America, Lister in South Africa, and Borel in France, have shown upon large bodies of men that dosages of 4,000 millions of each of at least six different strains, or a total of 24,000 million pneumococci, can be given with impunity, and are necessary, according to laboratory tests, for the production of high immunity in these cases. I think clinical experience will show that, except in the case of very highly susceptible people like the black races, upon whom most of these observations were made, quite such large dosages are unnecessary, and that a total of 4,000-5,000 million autogenous pneumococci, with perhaps the addition of similar dosages of one or two of the more dangerous and common strains of the country, will suffice to establish good immunity for at least twelve months. I claim that in none of my numerous writings during the past twelve years on the subject of vaccine treatment have I misled my readers upon a single important question. I hope to maintain this record, and trust my readers will recognize my right to be included within the category of the last line of the old Persian proverb standing at the head of this introduction, that they will accordingly pursue the methods and observe the rules I describe herein, and help to reconstitute vaccine treatment and

enable it to take its rightful position as the most truly scientific therapeutic agent in the doctor's armamentarium. Only this evening I was asked the following question by a local specialist in diseases of the ear, nose, and throat: "Why is it if you call in a bacteriologist in a case of otitis media that next morning you have a case of mastoid disease to deal with?" I answered his question by asking another, and it appeared that on one distant occasion he called in a bacteriologist, who gave a dose of vaccine to a case of otitis media, and that next morning mastoid disease developed, and that since then he had used no more vaccines. I asked further if he had ever seen this happen in cases which had not been vaccinated, and with his admission that he had done so I dropped the discussion. This illustrates well the truly illogical method by which not a few of high standing in the profession have assessed the value of vaccines. I do not say that some of its advocates have not had much to answer for in bringing it into disrepute, and would merely instance the extravagant claims made by certain of the earliest workers of cures brought about in 90 per cent. of cases of acne by the use of a staphylococcus vaccine alone: as the acne bacillus, and not the staphylococcus, is the true ætiological factor in at least 90 per cent. of cases, a staphylococcus vaccine cannot possibly suffice to cure the 90 per cent. of cases as claimed at the time.

During twelve years of specialization in this method of treatment I have in consultation been asked so many practical questions, and during my term of war service have seen the diffidence with which many doctors have undertaken the simple administration of vaccines when called upon to do so in their military capacities, that the conclusion has been forced upon me that a small

book adapted to their requirements has not yet been produced. I am now, therefore, endeavouring to repair the defect, and in these pages make no attempt to cater for brother-specialists or advanced laboratory workers: these will doubtless at times consider me unduly dogmatic and question the accuracy of my views; these, however, are at all times the product of considerable clinical experience, and in this their value lies. As briefly as I can, I simply endeavour to give such instructions and explanations as will enable the doctor, even in remote country districts, to give his patients the benefit of this now well proved and tested method of treatment, a method of treatment which, as I have often urged, is in no way designed to supplant the experience of past centuries, even with regard to the value of purely empirical remedies. Whether I have succeeded in my self-appointed task I can only leave to the judgment of those whom I have endeavoured to assist, and for fuller information refer them to my larger work, *Vaccine Therapy*. A special feature of the book to which I would draw attention is Chapter XVI of questions and answers: these questions are not concocted for the purpose, but are ones which I have been actually asked, and the answers are those I gave, now supplemented by references to the text. Should my readers so approve of the book and of this section in particular as to necessitate a second edition, I shall be very pleased to enlarge this chapter, and will at any time answer questions doctors may choose to put to me, if they on their part will undertake to inform me of the results thereby brought about.

In conclusion, if the doctor is to give his patient the fullest possible benefit, I would emphasize the absolute necessity of the closest possible co-operation between

himself and the bacteriologist or specialist. It does not suffice, as I point out in Chapter II, to send the latter a specimen well or ill chosen, well or ill adapted to the elucidation of the true bacteriology of the condition, for, after all, this is only part of the information necessary for the right treatment of the case ; whenever possible patient and bacteriologist should be brought together, with the view of the latter acquiring some idea of the soil with which he has to deal, and of the tillage to which it has in the past been subjected. In this way, and this way only, can Vaccine Treatment be utilized to full advantage, and the bacteriologist or specialist be enabled to advise the doctor aright with regard to the all-important question of dosage, intervals, and general conduct of the case.

I have to thank my friend Capt. F. L. Armitage, N.Z.M.C., late Bacteriologist in charge of New Zealand Stationary Hospital, France, for reading the manuscript for me, and for some useful little hints and suggestions.

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PRACTICAL VACCINE TREATMENT FOR THE GENERAL PRACTITIONER

CHAPTER I

CHIEFLY INTRODUCTORY AND DEFINITIVE

Definition of a Vaccine.—Sir Almroth Wright's definition, viz. that "Bacterial vaccines are sterilized and enumerated suspensions of bacteria which furnish, when they dissolve in the body, substances which stimulate the healthy tissues to a production of specific bacteriotoxins, substances which fasten upon and directly or indirectly contribute to the destruction of the corresponding bacteria," is the classical one; none the less it is very cumbrous, now inaccurate, and in the future likely to be even more so. It is faulty inasmuch as vaccines are not always sterilized; for instance, as we shall see later, the sensitized vaccines of Besredka and Broughton Alcock are not; nor are they always enumerated, though usually they are; they may be standardized by weighing, a more accurate method of estimating dosage, as is done in the preparation of some tuberculins and other vaccines. Quite possibly in the near future, when we shall be employing, as we certainly shall be doing, vaccines of the filterable viruses, some other method of standardization, based perhaps upon animal experiments, may have to be utilized.

More briefly and more accurately a **vaccine** may be described as "a suspension of bacteria living or dead, integral or disintegrated, in an inert fluid"; this latter being usually a weak solution (0·5–0·8 per cent.) of sodium chloride in water, to which as a rule a little antiseptic has been added so as to make the content up to 0·5 per cent. of carbolic acid, 0·3 per cent. of tricresol, or 0·04 of iodine. An **antibacterial serum**, or, as it is so often carelessly and incorrectly styled for shortness, an **antiserum**, is something quite different: it is the fluid portion, separated by coagulation, of the blood of an animal that contains various protective substances against a particular microbe or microbes, resulting from the methodical and long-continued injection of the animal with vaccines of that microbe or those microbes, or with their toxins, or with both. It is therefore essentially different from a vaccine, its action being due simply to the neutralization of the bacterial toxins circulating in the tissues by means of the corresponding antibodies of the serum. The immunity thus brought about is termed "passive," that brought about by vaccines is called "active." After this explanation I hope to hear much less frequently of doctors speaking of sera when they mean vaccines—a practice which has been strangely common in the past, and is always peculiarly irritating to those specializing in vaccine treatment.

The Aim of Vaccine Treatment.—From our definition of an antibacterial serum it appears that the injection of a vaccine into healthy tissues, for animals used in the production of such sera have to pass a searching medical examination, results in the elaboration in those tissues of certain protective substances, substances especially inimical to the health and well-being of these particular microbes with which the animal is being

injected. This is precisely the process which we endeavour to imitate when employing vaccines upon the human subject: we endeavour to exploit the healthy tissues in the interest of those which are infected and unhealthy. Healthy tissues are capable of responding strongly to stimuli of various kinds, unhealthy are not. When therefore we introduce into healthy tissues a certain number of microbes, dead or alive, these healthy tissues, in the attempt to protect themselves against the microbes or their products, elaborate so-called antibodies of various kinds, such as opsonins, agglutinins, bactericidins, and lysins, and it is a practically invariable rule that the elaboration of these substances is carried on to a degree far in excess of immediate requirements. Accordingly there is a considerable surplus which is carried, via the circulatory system, all over the body, and so, **if access be afforded them**, to the infected focus or foci, where they are available for the destruction of the microbes. This question of access is a very important one, to which insufficient attention frequently is given. It is of no avail to have a supply of antibodies more than sufficient for the destruction of all the infecting microbes if these latter are firmly barricaded in. Notable examples of this are afforded in such cases as those of (1) cerebro-spinal meningitis—here there may be, even just prior to death, a vast surplus of antibodies in the blood, but these are unable to find a way into the cerebro-spinal fluid; (2) the consolidation stage of pneumonia, when the microbes are fairly surrounded by a barrier of fibrin impenetrable, at that stage, to the circulating fluids of the body; and to a less degree in (3) acne, where the bacteria, strictly speaking, are in the main outside the body; and (4) fibrous sinuses, especially those produced by long-standing compound fractures of

bone and by various agencies of war. This obvious fact is very frequently forgotten, and for the omissions of the surgeon or doctor vaccine treatment has to bear the blame of failure and pay the penalty in contumely and neglect. There are various ways in which the defective circulation of the protective substances may be assisted, for instance by massage, by the application of dry heat, hot fomentations, and ultra-violet light, by surgical removal of the layers of coagulated blood and fibrin, as by scraping of a sinus, or by the introduction of Wright's citrated salt solution or of Dakin's fluid. Other means will readily occur to the mind of the reader, but when it comes to the practical application his memory and observation are only too liable to fail him.

Antibodies Specific.—The protective substances elaborated by the healthy tissues in response to the stimulus of the introduction of a certain microbe are in a very high degree specific—that is, they are of protective use only against that particular brand of microbe. For instance, it has been only too well proved clinically that the use of a vaccine of the true *Bacillus typhosus* is of avail only in so far as the *Bacillus typhosus* is concerned—for all practical purposes it affords no protection against the paratyphoid fevers; a vaccine of *Streptococcus faecalis* is of no avail against infections by the *Streptococcus pyogenes longus*; yet many doctors have been bitterly disappointed by the fact that the use of a vaccine of *Bacillus influenzæ* has entirely failed to protect a valued patient from a pneumococcal cold and a resultant fatal attack of pneumonia.

It thus follows that if it be desired to secure immunity against any particular microbe, a vaccine of that identical microbe and that microbe alone must

be employed: this is known as a simple vaccine. On the other hand, if immunity against several microbes be desired, then a vaccine now known as "combined" or "compound," and composed of each of these individual microbes, must be utilized. The first vaccine of this kind used was my "Combined Vaccine for Colds," which contained *B. influenzæ*, *pneumococcus*, *streptococcus*, *B. septus*, *M. catarrhalis*, and *B. of Friedländer*. Derided at the time by some or even many, imitations of it have been put on the market by various hospitals and well-known laboratories, and the most imperfect, deficient, and defective imitation of all has quite recently been adopted by the military authorities and compulsory universal use of it advocated for the army. Other well-known examples of compound vaccines are (1) the Vaccine T.A.B. of the Army, *i.e.* the vaccine for immunizing purposes against typhoid fever and the para-typhoids A and B; (2) Castellani's Tetra-vaccine against these three with the addition of cholera; and (3) his Pentavaccine, which is the "Tetra" with the addition of plague.

Careful laboratory tests upon the blood of men inoculated with these complex vaccines have shown that the degree of immunity exerted against the individual microbes is in no way inferior to that which would have resulted from the use of each vaccine separately, and there is the obvious great advantage of a considerable saving of time. The degree of local and constitutional disturbance resulting from the use of these complex vaccines is certainly greater than that due to the administration of a simple vaccine, but is at the same time so surprisingly small that no reduction of the individual dosages is required as a rule. Practical experience has amply confirmed the laboratory tests and borne witness

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to the ample immunity afforded from the use of compound vaccines, as we shall see later.

Sensitized Vaccines.—A vaccine against a certain microbe having its uses and a serum against that same microbe also perhaps having its uses, it occurred to Besredka at the Pasteur Institute that it might be well to combine the two in the same preparation instead of, as is sometimes done, administering the two separately. Besredka and Broughton Alcock therefore introduced what are known as **sensitized vaccines**. A suspension of bacteria and the corresponding antiserum are mixed and incubated together until the bacilli and the corresponding antibodies in the serum are so firmly bound together that repeated washing of the precipitated microbes after removal of the serum will not separate them. The bacteria and attached antibodies are then suspended as usual in salt solution, but without the addition of any antiseptic. The full technique will be described on p. 41. The sensitized vaccines of Besredka and Broughton Alcock are therefore in the living state; other workers have, however, modified them by killing the microbes either by heating them or adding antiseptic.

The idea in the introduction of these sensitized vaccines was that they would save the tissues from the necessity of elaborating the antibodies, that thereby local and constitutional disturbances would be minimized and a high degree of immunity more speedily attained. It was therefore hoped that they would be of especial value in the treatment of acute infections, as distinguished from the production of immunity against infection. This subject is considered fully on p. 43. I would only here point out that, inasmuch as our aim in administering a vaccine is to incite the production of antibodies, any

modification whereby the tissues are relieved in the whole or main of this task is faulty in conception. None the less, as we shall see, sensitized vaccines, or, as the Americans style them, **sero-bacterins**, have their uses.

Pathogenic Action of Bacteria : Exotoxins and Endotoxins.—The ill-effects produced by bacteria upon the human economy are almost entirely to be attributed to the poisons, or toxins as they are called, which they elaborate within the host and to very closely allied bodies. These toxins are of many kinds, each producing an effect peculiar to itself. They are, moreover, highly selective of the tissues which they attack. For instance, the toxin of the tetanus bacillus, known as tetanospasmin, produces its pathogenic effects solely through its combination with the nervous tissues, and so highly selective is it that it especially picks out the plates of the motor nerves, and passes up the nerve fibres to the motor ganglia in the anterior cornua of the spinal cord on that side of the body on which the lesion is situated. Later it affects the motor ganglia on the opposite side, and later still the sensory apparatus. When the tetanus bacillus is grown artificially in liquid culture media, it is found that considerable quantities of this tetanospasmin are to be found in the culture medium, even while the bacilli are still living and apparently still intact. The toxin would therefore appear to be excreted from the bacilli, be it into culture medium or the animal tissues of its host, during the life of the bacilli and as an essential part of their vital activity; it is accordingly known as an **exotoxin**. Instances of other bacilli which form exotoxins are the Klebs-Loeffler bacillus of diphtheria, the *B. botulinus* of food-poisoning, the *B. pestis* or plague bacillus, and Shiga's bacillus of dysentery. On the other hand, the toxins formed by

most bacteria are not excreted into the culture medium, either artificial or of the human host, as an essential part of the vital activity of the microbe. They do appear, slowly and in small quantities, in the culture medium, but only after the death and disintegration of some of the microbes. These toxins are therefore known as **endotoxins**. Among the varieties of bacteria which, so far as we know, form endotoxin and endotoxin alone, are the gonococcus, pneumococcus, staphylococcus, streptococcus, and *B. typhosus*.

A very few bacteria form both exotoxin and endotoxin, for instance, the plague bacillus or *B. pestis*.

It may be mentioned that some bacteria give rise to more than one variety of toxin, whether endotoxin or exotoxin ; for instance, the tetanus bacillus forms two endotoxins, the aforesaid tetanospasmin acting on nerve elements, and tetanolysin acting on the red blood corpuscles. The *B. diphtheriae* forms three toxins : (1) a general neuro-muscular toxin, the most potent ; (2) one producing local œdema, less potent ; (3) one producing paralysis, the least potent. Antidiphtheria serum contains large amounts of antibodies to the first only of these. The staphylococcus forms three toxins, one endotoxin and two exotoxins : (1) an endotoxin causative of pyrexia and local irritation ; (2) a haemolysin destructive of the red blood cells, exotoxin ; (3) a leucosidin destructive of the white blood cells, exotoxin. The antiserum contains antibodies only to (2) and (3).

This question of the nature of the toxin or toxins elaborated by any particular microbe is not one which can be lightly dismissed in vaccine treatment. Obviously the best means of dealing with any possible invasion by toxin is prevention of access or power of multiplication by the microbe forming it ; this is best done by

preventive inoculation with a vaccine, as in antityphoid or antiplague inoculation. But assuming that infection has occurred and that the nature of the infecting microbe has been ascertained, a consideration of the toxins elaborated by the microbe is not without bearing upon the question as to whether vaccine treatment is likely to be productive of benefit.

Assuming, for instance, that the **tetanus bacillus** is at work; now we know (1) that the chief toxin of the tetanus bacillus is exotoxic in nature, (2) that symptoms are due to the action of this toxin upon the nerve tissues with which it enters into fast combination, (3) that these symptoms only arise after an incubation period of some duration, during which the microbes have been multiplying and pouring their soluble toxins into the circulation. Assume also that it is proposed to deal with the condition by means of a vaccine—it is now necessary to know (1) whether by the administration of a vaccine any elaboration of antibodies capable of neutralizing the tetanospasmin is likely to occur; (2) if so, whether this will be achieved with a rapidity sufficient to neutralize the toxins in time to save the patient.

While the answer to the first of these questions is in the affirmative, the answer to the latter is an unqualified negative, so that the use of a vaccine in a case of developed tetanus is quite contra-indicated. The quantity of antitoxin needed can only be furnished through the agency of **antitetanic serum**. Whether a tetanus vaccine can be prepared which will be of any utility in cases of latent tetanus, and whether it will possess definite advantages over antitetanic serum, is quite another matter, and possibilities can be recognized.

Again, take the case of infection by **Shiga's bacillus**, which, as we have said, elaborates both an exotoxin, to

which most of the immediate symptoms are due, and also an endotoxin. What has been said with regard to vaccine treatment directed against the tetanus bacillus holds with equal truth here so far as the exotoxin is concerned, and relief from its effects is to be gained by the free use of a suitable **antidysenteric serum**. This serum will, however, be gravely lacking in antibodies capable of leading to the extinction of the infecting microbes, *i.e.* of what are known as lysins and bactericidins. A stimulus for the formation of these may, however, be sought, and possibly found, in the administration of a **vaccine**. These observations also hold with regard to the **plague bacillus**; and in the use either separately or in combination of antiserum and vaccine in such infections as these, possibilities of benefit can be seen to exist.

Finally, in the case of those bacteria which form endotoxin alone, it might be anticipated that serum treatment would have no place and that vaccine treatment alone is indicated. It must, however, be remembered that by the death and disintegration of these microbes the endotoxin is set free; for instance, the **pneumococcus** forms no trace even of soluble exotoxin, yet every doctor is familiar with the effects upon the heart of the endotoxin liberated on the death of the cocci. Neutralization of this toxin by anti-endotoxin contained in a suitable serum will obviously be of the greatest benefit, but unfortunately the preparation of such a serum has presented grave difficulties, which only after many years are being slowly overcome. In such infections as these the use of **vaccines** is therefore indicated as being likely to be productive of suitable immunizing stimuli.

One final point here needs consideration. It will be noticed that I have said **suitable** immunizing stimuli.

I have so phrased it of design, inasmuch as the administration of a vaccine, while leading to the elaboration of various antibodies, one or more of which may induce the death of the infecting microbe, may lead to the elaboration of one or more antibodies which by their action upon the bacteria may be inimical to the welfare of the patient. For instance, it is held that by the administration of a **cholera** vaccine the formation is induced of large quantities of an antibody known as **lysin** ; this leads to the rapid disintegration of the cholera vibrios, not within leucocytes or tissue cells, where the cholera endotoxin would be rapidly neutralized and broken down, but in regions whence it would pass into the circulating fluids of the body and so add to the condition of severe general toxæmia. This is at present largely theory, little clinical evidence of the value or otherwise of a cholera vaccine in cases of cholera being as yet available. Experience may prove the objection to be baseless and the possible danger over-estimated or even non-existent, but none the less these considerations will be taken into account by the wise man, and it will be admitted that vaccine treatment consists in something more than off-hand administration of a vaccine. It is necessary to know not only what are the means whereby the bacterial invaders attack the tissues, but also what are the effects likely to be produced by turning their own weapons upon them ; it is no use turning their own guns upon them if our ammunition does not fit. We must know therefore what toxins each microbe forms in the body, and how these toxins act ; we must also know what antibodies are likely to result from the use of a vaccine, how speedily they will be formed, and what will be the effects produced by their interaction.

Space for a detailed consideration of these points will be lacking in this small book, which, moreover, does not propose to deal with serum treatment. I must therefore content myself by indicating in these pages when a serum is to be preferred to a vaccine, or when it may be combined with it, and leave it to the reader to conclude that it is based upon such considerations as these that the advice is given. If he desire to pursue the matter further, he must refer to large books on immunity such as that of Kolmer, or await the next edition of my larger work, *Vaccine Therapy*.

CHAPTER II

THE TAKING OF SPECIMENS

A PRELIMINARY, and a most important preliminary step to the preparation of any vaccine is the collection of the "materies morbi." Again would I urge the extreme advisability of the doctor, whenever it can possibly be done, first discussing every aspect of the case and putting the expert in full possession of the clinical history, and then giving him the opportunity of collecting his own specimen in his own way and of surveying critically the tissues to which the stimulus is to be applied. I am fully aware that this is not always possible, so I shall now endeavour to point out how the doctor can best minimize the defect. The specimen when taken should be delivered at the laboratory with all possible speed, in order that the multiplication of the germs, and especially that multiplication of one variety of germ at the expense of another, may be kept at the lowest possible level, and also in order to anticipate the death of such fragile organisms as the meningococcus, *B. influenzæ*, or dysentery bacillus. Accompanying it should be a covering letter containing a full clinical history of the case, and any details which may be of possible use to the pathologist. It should hardly be necessary to point out that all collecting apparatus should be perfectly sterile and should, whenever possible, be supplied from the laboratory, and that no antiseptic should ever be added

to a specimen. The actual collection should be carried out with great care and with precautions appropriate to the case, as otherwise the work of the bacteriologist will be needlessly increased and perhaps even rendered valueless. For instance, the *Staphylococcus albus epidermidis* is present in all skins and is said to be perfectly harmless and a vaccine of it to possess no immunizing power. If then the skin be not cleansed carefully with dilute tincture of iodine, acetone soap, or other weak disinfectant prior to taking a culture of serum from a weeping eczema or of pus from a superficial sinus, the bacteriologist will almost certainly find this microbe growing in his culture, and perhaps be left guessing as to whether this microbe, which it is almost impossible to differentiate with certainty from pathogenic forms of the *Staphylococcus albus*, may not be concerned in the lesion ; for, remember, he has not seen the patient, and has only such clinical notes of the case as those with which you have furnished him, and I leave it to your consciences to say how copious these usually are. It may not be amiss, and may help to impress the point I am labouring more clearly on your minds, if I give one or two examples actually taken from my own experience of what is sometimes expected of the bacteriologist. Forwarded to me, a dried smear of blood on a glass slide, wrapped up in cotton-wool in a small cardboard box crushed and broken—with the request that I should prepare a vaccine : only information given, “ blood from a case of malaria.”

Again, sent to me, about half a cubic centimetre of blood in a piece of glass tubing 2 in. long, $\frac{1}{4}$ in. in diameter, drawn out at the ends, one of these left open, at the other an attempt had been made at sealing, obviously with the aid of a candle or match, resulting in

this end of the tube being blocked with semi-charred blood. Request: "make blood culture and prepare vaccine." Information: "case of septicæmia."

Of course these two are extreme instances displaying a depth of ignorance almost incredible; none the less, it is quite a rarity to receive both a properly collected specimen and such clinical data as would enable me to prepare a proper vaccine in dilutions suitable to the case, and to give such advice as is requested for the conduct of the case. I therefore give here two specimens of forms properly filled in, such as should accompany the given pathological material.

FORM I

Name of patient.—Sarah Evans. Married. Age 38.

Material.—Pus from cervix uteri.

How taken.—On sterile swab through a vaginal speculum, first thing in the morning, 12 hours after treatment.

Disease.—Endometritis, gonococcal in origin.

Clinical Data.—Patient was quite well until three months ago, when abortion occurred at six months. She has three healthy living children, no previous abortions. The uterus apparently involuted satisfactorily, and recovery appeared to be complete, but a purulent discharge was noticed a month ago, and has not improved under treatment with antiseptic douches. General condition good. The husband has been away from home for a month, but in a letter to me denies that he has or has had any venereal trouble.

Investigation required.—Ascertain nature of infective agent if any, and prepare vaccine if advisable.

In this statement there is not a single unnecessary fact stated, every one is of great value to the bacteriologist, but I venture to say that the latter does not receive such a form with one specimen in 1,000. I freely admit that such a lengthy account is not always required, but I will ask my readers what information

do they send with a specimen of sputum beyond such as the following: "Sputum from A. A.—case of acute bronchitis"? To the bacteriologist the specimen more often than not is one rather of saliva than of bronchial secretion, the narrow-necked bottle is full of the nasty mess, some of which is escaping past an ill-fitting cork, which in turn is failing to prevent the access of organisms from the air and packing materials. Instead of this the specimen should have been contained in a wide-necked bottle, closed either with a glass stopper or well-fitting cork, it should have amounted at the most to a dessert-spoonful, and should really have been bronchial secretion as far as possible, and not one part mixed with nine parts of saliva from a mouth full of carious teeth and with gums far advanced in pyorrhœa.

The information which should have accompanied it I give in Form II.

FORM II

Name.—Alice Jones.

Age.—27 years.

Material.—Bronchial secretion.

How taken.—On awakening, after the teeth and gums had been brushed and the mouth well washed out with cold boiled water.

Disease.—Acute bronchitis.

Clinical Data.—The attack, the first of the kind, began suddenly a month ago, and apparently began as such, and despite drugs and confinement to bed in a warm airy room progress is very slow. The general condition is poor.

Required.—Nature of infective organisms, prepare vaccine if advisable, and advise as to treatment.

Again this does not contain a single bit of information valueless to the pathologist if he is to carry out properly the doctor's requirements. It will perhaps induce my readers to pay much more heed to this matter and devote more time, attention, and ingenuity to the proper

filling-in of the covering letter accompanying any specimens he may send in the future if I analyse Form II critically and point out the value to the bacteriologist of each item of contained information.

(a) The name or initials obviously is necessary for the proper identification of the case, both in the present and future ; the full name is to be preferred to initials, for two people with the same initials are not uncommon.

(b) The age is necessary, both for assessing the advisability of vaccine treatment and for the estimation of the appropriate dosage.

(c) Some statement of the source is helpful ; inasmuch as nasal and bronchial secretions differ considerably as a rule in density of infection, the bacteriologist is thereby assisted in the preparation of his smears and culture plates.

(d) The details as to how the specimen was taken assist the bacteriologist considerably in assessing not only the density of the bronchial infection, but in arriving at some definite conclusion as to the bacteriological condition of the upper respiratory tract along which the sputum has been voided. For instance, if after the precautions detailed he finds in the specimen many of the bacteria commonly associated with tonsillitis or pyorrhœa, he is enabled to warn the doctor of this, and point out the necessity of adequate treatment of this infection, as otherwise the patient incurs the additional danger of becoming a chronic bronchitic or of suffering from the other various disorders which are such common sequelæ of neglected pyorrhœa : he is also assisted in forming a correct idea as to the proper constituents of the proposed vaccine.

(e) This clinical statement of the attack is absolutely essential if the bacteriologist is to be enabled

to assess with any accuracy the probable need, value, and method of use of the vaccine. The fact that the attack is a first one might incline him to the feeling that an expensive vaccine is hardly indicated in this case ; as a corrective to this view he learns that, despite the patient having received proper medical treatment and careful nursing, the condition has not improved as it ought to have done with a first attack and in a plain straightforward case which did not arise from any precedent or chronic infection of the upper respiratory tract. Progress being slow and the general condition poor, the bacteriologist is led to conclude that further ground should not be lost, lest worse befall the patient, either in the way of an attack of pneumonia or of the disease becoming chronic. He is now therefore in a position to advise that vaccine treatment be adopted, and that a moderate initial dosage be employed, for while there is no great urgency and nothing is to be gained by upsetting the patient with large doses, neither is anything to be gained by beginning with too small trial dosages.

Assuming that the patient makes a good recovery, from the information supplied the bacteriologist is also in a position to advise as to subsequent short courses of preventive inoculation. As the attack at the age of 27 was the first of the kind, the patient obviously is not seriously predisposed to bronchial trouble—assuming that the pneumococcus is the only infective agent found, the conclusion also is arrived at that the patient is not susceptible to the catarrhal organisms in general—so that, even if preventive inoculation for the future be decided on, the incorporation in the vaccine of the other catarrhal organisms would certainly be justifiable, but equally certainly is not a necessity. In a case such

as this, I should advise a short course of preventive inoculation with moderately high dosages at the end of the following autumn, so as to afford the patient every chance of escaping a fresh attack so soon after one from which recovery has been delayed. At the same time, if the patient showed any opposition, this procedure might well be waived.

I shall now proceed to the description of the manner in which specimens from the more common sources should be collected.

(i) **Nasal Secretion.**—Swabs from the middle turbinate bones of healthy individuals should be quite or very nearly sterile. In taking swabs from this area, the main danger of introducing contamination arises from the swab, especially in the act of withdrawal, coming into contact with the vibrissæ. Such contamination is liable to be especially troublesome to the bacteriologist as the organisms on the vibrissæ are derived from the inspired air, and therefore very likely to contain members of the rapidly growing motile sporing microbes, such as *B. subtilis*; one of these on the culture plate means total loss of the plate, so rapid is the growth of these motile organisms.

It is therefore necessary to take swabs from the mucous membrane of the middle turbinal bone through a sterilized nasal speculum, every care being taken to avoid contact with the vibrissæ as the swab is being withdrawn. If after these precautions anything like a free growth of a pathogenic organism is obtained from an area which normally should be sterile, the evidence of infection and of the nature of the infective organism is considerably strengthened. In passing I may remark that the common way of collecting nasal mucus is for the patient to blow it out on to a clean (!) handkerchief,

or in a more refined way to close one nostril with a finger and blow the secretion down the other direct into a wide-necked bottle. If swab and speculum are lacking, the second of these ways is distinctly to be preferred.

(2) **Post-nasal and Post-pharyngeal Secretion.**—Swabs are best taken with the aid of a West's speculum—in the former case especially one must be careful to get into the post-nasal space without touching the uvula or anterior surface of the soft palate. The importance of avoiding contamination is well illustrated by Gordon's observation that the streptococci present even in the normal healthy mouth are so inimical to the meningococcus, that culture plates have to be prepared immediately the swab is taken, as otherwise little or no growth of the meningococcus will be obtained, even when this microbe is present in the post-nasal space in enormous numbers, the streptococci being correspondingly few.

Throat swabs for membranous or ulcerative conditions will of course be taken from the affected areas ; when possible it is as well for the collector to inseminate a culture tube of blood agar and of blood serum immediately the swab is taken, and to forward both swab and culture tubes to the laboratory with all convenient speed. I may here point out the necessity of the collector either filling in fully a covering note of the clinical condition and the precise investigations he desires to be carried out, or of leaving the latter entirely to the bacteriologist, merely requesting information as to the nature of the infecting organisms. It is not fair to ask for an examination solely regarding the presence of the Klebs-Loeffler bacillus and to be angry because the bacteriologist fails to report the presence of the organisms of a Vincent's angina or of an acute streptococcal infection.

(3) **The Bronchial Secretion.**—Owing to the operative difficulties of the doctor taking direct swabs from the mucous membrane of the bronchi, reliance has to be placed upon the sputum voided by the patient as a fair specimen of the bronchial secretion. It has to be remembered that this sputum has to pass along the length of the upper respiratory tract, and that there is nothing to prevent the picking up of gross contamination on its upward way; inasmuch as this cannot be totally obviated, it devolves upon the doctor to minimize the risk as much as possible, and upon the bacteriologist to take such steps as are possible to free the chosen sample from the acquired contamination, viz. by several washings in sterile salt solution, and to make allowances for what cannot in this way be removed. It is also to be remembered that one specimen can hardly with safety be assumed to be representative, either of the whole bronchial secretion or of that secreted at the focus or foci of infection. Neither doctor nor bacteriologist therefore should be satisfied with a single specimen; two are to be preferred to one, and with three the margin for error is still further reduced.

Prior to instructing the patient how to take the specimen, it behoves the doctor to make a careful scrutiny of the upper passages for polypi, adenoids, infected tonsils, gums, and teeth. If foci of gross infection exist in the upper passages, appropriate treatment of these is strongly indicated prior to vaccine treatment of infected foci in the bronchi or lungs, unless the latter condition be one demanding urgent attention. It is little use endeavouring to sterilize the lower air-passages if follicular tonsillitis or pyorrhœa be existent above. Personally I refuse even to make the attempt, as doctor and patient alike are certain to be disappointed with

the result and vaccine treatment is sure to be brought into disrepute.

Should the case, however, be one of such urgency that delay is inadmissible or facilities for the proper treatment of the patient be non-existent, then the precautions I am about to detail must be carried out with the greater thoroughness. The doctor should furnish the patient with two or even three sterilized wide-necked bottles, fitted either with glass stoppers, which are to be preferred, or with well-fitting corks of rubber or bark. The bottles should bear the name of the patient. He should instruct the patient to procure a new, moderately hard toothbrush, to place this overnight by his bedside along with one of the bottles and a covered jug of boiled water. On waking in the morning the patient is to cleanse his teeth and gums thoroughly with the new brush and boiled water; no powder or antiseptic is to be employed. This done, the throat is to be gargled and the mouth rinsed out; two or three mouthfuls of the sterile water should then be swallowed and the patient give a good cough. The secretion so brought up is to be voided directly into the bottle, which should not have been unstoppered prior to this. The specimen should be forwarded to the laboratory with the least possible delay, to minimize the risk on the one hand of death of such delicate organisms as the *B. influenzae* or meningococcus, and on the other hand of the multiplication, which is especially likely to occur in hot weather of the more sturdy microbes, and especially of contaminating air bacteria, such as *B. subtilis*. At the same time it is worthy of note that I have made vaccines with complete success from specimens of sputum sent from Afghanistan and S. Africa, and of urine from China. The second specimen should be collected and dealt

with in precisely the same manner on the morning following.

(4) **Urine.**—Whether the patient be male or female, a sterile catheter should be used for the collection of the specimen. This preferably should be done early in the morning, as in this way a sample is procured of the whole excretion of the kidney during ten to twelve hours. The flow of the urine should be directed into a sterile bottle, and not into one merely rinsed out with tap water or into a dirty utensil. The doctor should remember that the *B. proteus* is a frequent inhabitant of tap water, and whereas it was formerly looked upon as non-pathogenic, it is now known occasionally to give rise to cystitis. If, therefore, the bottle be washed out with tap water containing it in any numbers, the bacteriologist will certainly find it in his cultures, and have great difficulty perhaps in deciding whether it is in any way responsible for the condition which he has been called upon to investigate. If members of the typhoid group are suspected to be present, the sterile bottle should be one-quarter filled with sterile bile, and the patient should micturate directly into this bottle, after first flushing out the urethra with a small portion of the urine contained in his bladder. Under special conditions it may be necessary to employ a different technique; for instance, cystitis may be known to exist and infective nephritis suspected. In this case it will be necessary first to wash out the bladder thoroughly, then if possible to catheterize one or both ureters.

(5) **Fæces.**—Upon the disappointing results commonly obtained from bacteriological cultures of the fæces, especially in cases of typhoid fever and dysentery, considerable light has very recently been shed. Despite the immense amount of attention which has been directed

towards the elaboration of highly selective and favourable culture media, cultures have been so frequently negative when positive ones have been anticipated with the utmost confidence, that grave doubts have arisen as to the viability and powers of resistance of the causative organisms in some of the common infective diseases of the intestinal tract, and it has been ascertained that as with the amoebæ of dysentery so with the bacilli of typhoid fever and dysentery. While these microbes will live for weeks and even months in artificial culture, they are liable to die off in the fæces with such extreme rapidity that a growth may not be obtained if the preparation of the culture plates is deferred for more than four hours after the voiding of the fæces. As in the case of the meningococcus, so with these residents of the intestinal tract, the most satisfactory technique is that wherein direct smears are taken by means of a suitable instrument from the mucous membrane of the rectum or sigmoid, and cultures are at once made upon appropriate media. In this way the percentage of failures is reduced almost to zero. Quite satisfactory results may be anticipated if a sterile throat swab be inserted per rectum by means of gentle and continuous pressure and a slight rotatory movement communicated to the swab in such a direction that the roll of cotton-wool is not unwrapped from the wire. The swab having been inserted to its full length and gently rotated is then withdrawn, one or two plates of the selected media may then be inseminated by the doctor if they are available, and both swab and plates should then be sent to the laboratory with as little delay as possible.

When the question of the possible existence of a "carrier" has arisen, the selection of a proper specimen of fæces assumes even an added importance. The dis-

charge of the bacteria may be very intermittent both via the kidneys and bowels, so that repeated examinations may have to be made before a positive culture is obtained. It is to be noted that dysentery bacilli seldom occur in the truly faecal stool, even when the disease is active, while they occur in vast numbers in the bloody mucous ejecta. The above recent discoveries in regard to the cultural exigencies of the meningococcus and dysentery bacilli lend further strong support to my repeated plea for the establishment of the closest possible co-operation as a matter of routine between doctor and bacteriologist.

(6) **The Blood.**—The taking of blood cultures, as well as of those of the cerebro-spinal fluid, pleuritic fluid, and pus from joints, is best left to the bacteriologist himself, or at least should be done in his presence. I am not insinuating that the great majority of doctors are not fully competent to do the work, but let it be remembered that one microbe introduced into the specimen from the skin, air, or instruments will or may suffice entirely to upset the future work and observations of the bacteriologist ; the responsibility for such a mishap is best fastened upon his own shoulders. Strict asepticity must be observed throughout, and an adequate supply of the material must be furnished. Many a blood culture may prove negative when 5 cubic centimetres of blood are taken and introduced into the culture medium which would prove positive if this quantity were increased to 10 or 20 cubic centimetres. The largest of these quantities is just as easily abstracted from the median cephalic or median basilic vein as is the smallest, and it makes little or no difference to the patient. This being so, I advise that after the superjacent skin has been thoroughly cleansed with strong tincture of iodine,

a tourniquet applied just below the shoulder, and the selected vein pierced with the needle of a carefully sterilized 25 c.c. all-glass syringe, at least 20 c.c. of blood should be abstracted, the tourniquet at once released, the needle withdrawn, and the blood ejected into the flask of carefully sterilized culture fluid with which the doctor has been provided. This done, the rubber cork should at once be replaced in the flask to prevent the possible access of a single microbe from the air; the flask should be returned to the laboratory and placed in the incubator with all possible speed. Upon the question as to what should be the composition of the culture fluid in the flask, the nature of the supposed infective agent is not without some bearing. For instance, if the pneumococcus be suspected, the flask should hold 200 cubic centimetres of broth containing 5 per cent. of sodium chloride, 1 per cent. of peptone, and 2 per cent. of glucose, the high percentage of sodium chloride herein counteracting the bactericidal action of the blood; if the *B. typhosus*, 100-200 c.c. of sterile bile or of McConkey's glucose bile salt medium. If it be preferred, the syringe may well be omitted, 4 or 5 inches of sterile rubber tubing being affixed to the needle, and the blood at the increased pressure due to the tourniquet being allowed to flow freely into the flask of culture medium until a sufficient quantity has passed. If the doctor is his own bacteriologist, he should remember to examine the flask and make subcultures at the end of twenty-four, forty-eight, and seventy-two hours, and daily thereafter, and not to conclude that any blood culture is negative until the lapse of seven days.

Not only is the number of bacteria initially present in the 20 c.c. of blood likely to be small, but the bactericidal and inhibitory power of this large quantity of

blood is also to be taken into consideration. Furthermore, bacteria, even when isolated from the blood, show a delicacy of growth somewhat unusual to them until they have been subcultured a few times. All these factors tend to retard the appearance of any growth in the blood cultures. Of course the effect of these unfavourable factors is not always in evidence, especially if the medium be modified to the advantage of the particular microbe. Thus I have often obtained free growth in subcultures made from the blood after only 12-18 hours' incubation.

(7) The **cerebro-spinal fluid** should always be collected in two strong sterile glass tubes fitted with sterile rubber corks; the first few cubic centimetres of the fluid are usually blood-stained, and should be placed in the one tube, the subsequent portion in the second tube. For the technique of the operation the reader is referred to any well-known text-book on surgery. I would only add that I distinctly favour its performance under light general anæsthesia, as I have seen some rare bungles under local anæsthetics.

Finally, I may point out that if a vaccine is to be prepared for a case of glanders, actinomycosis, or even a simple boil, it is not advisable to collect on a sterile swab the free discharge from an open lesion, for this will inevitably be secondarily infected by the *Staphylococcus albus epidermidis*, and probably by air organisms. The skin over a mature nodule should be painted with tincture of iodine, when this is quite dry the nodule should be incised freely, the swab inserted into the centre of the infected area, twisted round until well saturated or until a fair amount of pus or serum adheres; and placed in a tube with a good cork or cap of tinfoil to prevent drying.

CHAPTER III

PREPARATION OF THE VACCINE

My design in this little book being, as I have said, mainly to assist the general practitioner in the actual treatment of his cases and, while affording him some guidance in all that appertains to the same, not to give any detailed account of the technical procedures which the more properly fall within the realm of the bacteriologist, I do not propose to discuss fully the technicalities of vaccine preparation. As, however, there are some who, either from election or through necessity, do prepare their own vaccines, I will briefly refer to certain points connected with the manufacture of the vaccine. We will assume that, as a result of the good advice given in Chapter II, the right kind of specimen has been taken in the right kind of way. The first thing now to be done is to make a thorough microscopic examination of it, both with unstained and with suitably stained preparations. By doing this we acquire a good preliminary idea of the nature and density of the infection, and are enabled to select the appropriate culture media and sow the plates in such a way that discrete colonies of the various microbes are ensured. These without any subculturing may then be utilized to inseminate fresh plates for the preparation of the bacterial emulsion.

Failure in making these direct examinations of the *materies morbi* is responsible for no small proportion of

the failures in vaccine treatment. The pus from a case of acne is planted on culture plates, a staphylococcus grown, vaccine made, and patient treated, with resultant failure, ascribed of course to vaccine treatment ; whereas if a specimen of the pus had been properly stained and examined in the first place, the information would at once have been forthcoming that the acne bacillus was the chief infective agent, and that special culture media and special methods had to be utilized for its isolation and subsequent culture. Within my own experience this omission has been so often made that I feel I can hardly too strongly emphasize the dangers that are likely to arise from it. Another point which has frequently come to my notice is the extraordinary laxity displayed, even by those who have had a fair amount of laboratory training, in the choice of appropriate culture media.

Many seem to think that with the insemination of agar plates and blood-serum tubes and aerobic incubation thereof, their cultural efforts are completed. There is no medium universally adapted to the isolation of the pathogenic bacteria ; the nearest approach to such a one is Gordon and Hine's Trypagar, to which sufficient sterile citrated **human** blood has been added to impart a good deep colour, and not a mere tinge of blood. I do not consider that the blood of animals is nearly so well suited as human blood for the isolation and culture of microbes infecting man.

Anaerobic as well as aerobic conditions are to be maintained with the cultures ; failure to employ anaerobic conditions being a source of erroneous diagnosis of the infective agent, which should never occur. For the composition of the various cultural media which may be required the reader must refer to the larger and more recent textbooks on bacteriology. In most cases

an adequate growth of the selected microbe will appear after eighteen hours' incubation. The shorter the period of incubation when a vaccine is to be prepared the better, for sometimes even prior to eighteen hours some bacteria tend to die ; this leads to the liberation of their endotoxins and the consequent production of a vaccine with more or less markedly toxic properties. When sufficient growth has appeared on the plates, a small quantity (2-3 c.c.) of sterile normal salt solution is distributed over the surface of the plate, and by means of a thin bent glass or preferably aluminium rod the bacteria are emulsified as thoroughly as possible, and the mixture pipetted into a perfectly clean centrifuge tube ; by the addition of a little fresh salt solution the residual growth on the plate may be removed and added to the first portion in the centrifuge tube. This is then placed in the centrifuge and centrifuged till the bacteria are all thrown down ; the supernatant salt solution is then pipetted off and a fresh quantity added, with which the growth is thoroughly mixed. The object in removing the suspending fluid is that experience has shown that the small quantity of blood serum, both unaltered and altered by the bacterial growth, as well as the other moisture of the plate, contains bodies (endo- and exo-toxins of the bacteria, etc.) which add to the toxicity of the vaccine. Some bacteriologists, with the view to the more complete removal of these, subject the bacilli to a second washing. The growth having been re-emulsified as thoroughly as possible, it is often centrifuged for a few seconds at a low speed to deposit all foreign matter and clumps of bacteria. Some microbes, however, such as certain strains of *M. catarrhalis*, *streptococcus*, and even *pneumococcus* and *staphylococcus*, spontaneously agglutinate with such rapidity that this process cannot

be carried out, for practically the whole of the vaccine would thus be wasted.

The emulsion, which should now be uniform and free from clumps, is pipetted into a fresh receptacle and is ready for standardization and sterilization.

It will be evident that if the foregoing instructions be carried out, none but primary or secondary cultures of any microbe will enter into the composition of any of our vaccines. This is a point of the very greatest importance, which I have insisted on in all my writings, as in this way only—with possibly a few exceptions, as in the case of the *B. typhosus*—can a vaccine possessing the highest possible immunizing powers be prepared. It is far better practice, for instance, to prepare a *B. influenzae* vaccine from a perfectly freshly isolated culture, containing a few pneumococci or *M. catarrhalis* as impurity, than from an absolutely pure culture which has necessitated several subcultures to ensure this purity. While it is true that laboratory tests may show little falling off in the antigenic value, it must be remembered that (1) these tests can seldom be carried out on the finished vaccine, especially if heat be necessary for sterilization; (2) the only reliable tests of immunizing power are those carried out upon human beings, and not upon animals or in the test-tube. As my own experience of clinical vaccine treatment has accumulated, the more firmly rooted has become the reliance I have placed upon primary or secondary cultures as my immunizing agents.

Standardization of the Vaccine.—Numerous methods have been devised for estimating the number of microbes contained in each cubic centimetre. Among these are (1) counting, (2) by comparison of the opacity against a standard emulsion, (3) measuring, (4) weighing. For each of these methods certain advantages are claimed.

The *counting* may be done in various ways. In Wright's method an unknown quantity of sterile citrated salt solution, greater or less in amount, according to the density of the emulsion, is first taken up into a fine capillary pipette, then a measured small quantity of blood from a pricked ear or finger-tip, finally the same volume of the emulsion ; these are then expelled on to the surface of a clean microscope slide and thoroughly mixed by the alternate sucking up and expulsion of the whole into the capillary pipette. This being done about a dozen times, the whole is once more aspirated into the pipette, and a small drop of the mixture placed on each of two clean slides ; this drop is then spread exactly as in making a blood-smear, allowed to dry, and stained with Leishman's stain. By means of an oil emulsion lens the number of bacteria and red blood cells respectively in 20-30 fields of the microscope are counted : it being assumed that 5,500 millions of red cells are present in each cubic centimetre of blood, a simple sum in proportion gives the number of bacteria contained in that quantity of emulsion.

In another method of counting, the Thoma-Leiss apparatus for counting the red blood corpuscles is utilized, and the procedure is precisely the same. If the bacteria are motile, a necessary preliminary is that they should be rendered immotile, this being done by first mixing equal small quantities of the emulsion and a formalinized salt solution, to which a little aqueous methylene blue or methyl violet stain may be added if desired ; in this case of course the result of the count must be multiplied by two.

Critics claim that in both these methods there exists a considerable margin of error, the second method being the more reliable. If, however, the various steps are

carried out with due care, the result is, I am convinced, quite sufficiently accurate for all purposes. They are, however, somewhat laborious, and especially the first requires a considerable amount of practice and dexterity.

The method of *comparison of opacity* with a standard emulsion is certainly easy and quick, only requiring that into a graduated container precisely similar to the one containing the standard emulsion a known small volume of the emulsion to be standardized should be placed; diluting fluid is added gradually and thoroughly mixed with the emulsion, comparison of the two for opacity being made against a dark background after each addition of diluent, this being continued till the two opacities correspond. This method is open to very grave error, for the operator is, as a rule, in possession of a standardized emulsion of only one variety of microbe, usually a staphylococcus. Now, emulsions of, say, *B. influenzæ*, *B. coli*, staphylococcus, and meningococcus of the same strength possess very different opacities, or to put it in another way, emulsions of these of the same opacity contain very different numbers of microbes.

Those, therefore, who employ this method should be in possession of standardized emulsions of the various microbes, but so far as I know this is not the case. This is a very favourite method of American workers, and for the reason given I regard it with very great disfavour, and therefore look on the American vaccines on the market with considerable suspicion.

For the method of standardization by *measuring* it is a preliminary necessity to have accurately graduated centrifuge tubes, and ascertain how many millions of *each* variety of microbe correspond to one of these

graduations; it is also essential to prepare emulsions free from such foreign matter as small masses of the medium. This is a very easy, quick, and reliable method once the necessary preliminary standardizations have been carried out with the necessary care.

I know, for example, that if I place in a certain centrifuge tube an emulsion of *B. coli* and employ a speed of 3,000 revolutions per minute for five minutes, that each division on the tube occupied by the mass of bacteria so thrown down corresponds to 15,000 million *B. coli*; if therefore four divisions are occupied, I have a total of 60,000 millions of *B. coli*; if now I thoroughly mix the deposit with 60 c.c. of diluent, I know I have a suspension containing 1,000 million per cubic centimetre. By once standardizing other graduated tubes in a similar way for *B. influenzæ*, *staphylococcus*, etc., it is thus possible to estimate the total numbers of any given microbe at our disposal in precisely five minutes—with a very slight margin of error.

The method of standardization by *weighing* is also capable of great accuracy, but takes considerable time and care to carry out. The emulsion of bacteria must be made with perfectly pure distilled water, then thrown down by centrifugalizing, washed with distilled water and again thrown down, this process being repeated two or three times. The bacteria are then pipetted off into a small receiver, whose weight is accurately known, very carefully and very thoroughly dried in a vacuum at a temperature of 50° C. until the weight is constant. By subtracting the weight of the container, the weight of dry bacterial substance is arrived at.

A milligram of the following dry bacteria is stated to correspond in numbers as follows:

Staphylococcus	3,000 millions	.
Streptococcus	3,400	„
Gonococcus	4,500	„
B. coli	6,400	„
B. typhosus	8,000	„
Tubercle bacillus	4,500	„

I have never employed this method, except in the case of the tubercle bacillus, and accept no responsibility for the accuracy of the figures; in fact I cannot believe that a staphylococcus weighs nearly three times as much as a typhoid bacillus, which observations of my own have shown to be larger in bulk by about 50 per cent.

Sterilization of the Vaccine.—Having standardized our emulsion, we can proceed to its sterilization. This is done by means either of heat or antiseptic, or by a combination of the two. Heat is objected to on the grounds that a temperature necessary to bring about the death of many microbes is prejudicial to the vaccine, impairing its efficiency and keeping powers, and increasing its toxicity. If reliance is to be placed on heat alone, the temperature must be adjusted to the microbe—for instance, sterility of a vaccine of *B. typhosus* should be brought about by maintaining the emulsion at a temperature of 53° C. for thirty minutes; while the death of all the individuals of an emulsion of *Staphylococcus aureus* cannot be ensured by a temperature of 60° C. acting for thirty minutes, a few apparently more heat-resisting individuals may not be killed therein at a temperature less than 63° C. It has thus come about that reliance is seldom placed on heat alone, but after half an hour's exposure the vaccine is allowed to get quite cold, when sufficient carbolic acid is added to make

0·5 per cent. present, or of tricresol up to 0·3 per cent. Iodine to an amount varying between 0·02 and 0·04 per cent. is stated by Ranque and Senez not only to ensure perfect sterility, but also to reduce toxicity of the vaccine to a marked degree.

The practice has become increasingly common of avoiding the heating of a vaccine whenever possible, and of placing reliance upon the addition of antiseptic alone. It has been found that the addition of the above quantities of antiseptic to bacterial emulsions of moderate density suffices in most cases to bring about sterility in twelve hours, and that the immunizing and keeping powers of the vaccine suffer less impairment. Whatever be the method employed for sterilization, the fact that sterility has been secured may be verified by adding a small quantity of the finished product to tubes of appropriate liquid media and incubating these under both aerobic and anaerobic conditions for at least twenty-four hours; subcultures should then be made on solid media; incubation of these for twenty-four hours again under aerobic and anaerobic conditions should suffice to determine the sterility of the vaccine.

It must be mentioned that not all vaccines are sterilized either wholly or in part; for instance, Besredka's sensitized vaccines and Strong's antiplague vaccine are not sterilized at all, while Castellani's antityphoid vaccine is subjected to a degree of heat sufficient only to reduce the virulence of the microbes.

Storing the Vaccine.—The vaccine having been counted and sterilized, it remains that it should be placed in sterile receivers in which it is free from danger of subsequent contamination.

Formerly, when Germany supplied us with bulbs in a great variety of pretty colours, it was the custom to

make several dilutions of the vaccine, and place each dilution in a different coloured bulb: for instance, 1 c.c. of a dilution of, say, 100 millions per c.c. was pipetted into a number of brown bulbs, blue bulbs containing 1 c.c. of the 250 million per c.c. strength, and so on. Now it is more customary to limit the number of dilutions, say, to two, and place 20-25 c.c. of each dilution in a sterile bottle fitted with a rubber cork or a rubber cap which is wired on and coated with a layer of paraffin. Each method has its advantages and disadvantages.

If the vaccine be put up in sealed ampoules, there is no danger of the dose being contaminated from the air—there may, however, be a slight difficulty in breaking the neck of the ampoule, but not if a slight scratch be first made with a file—and with all coloured glasses, except brown, there is a risk of the alkaline pigment dissolving out and rendering the vaccine turbid and discoloured.

If it be put up in bottles of 20-25 c.c. capacity, these should be sterilized, nearly filled with vaccine, and closed with rubber corks or with rubber caps, these being carefully secured with copper wire and then dipped into melted hard paraffin or a mixture of one part of 2 per cent. tincture of iodine with two parts of flexible collodion. If a rubber cork be employed, as this has to be removed each time it is desired to abstract a dose of the vaccine, there is a slight danger of sporing organisms getting in from the air; if, however, the cork be replaced promptly and ordinary care taken, the risk of the vaccine being contaminated and made unfit for use is practically negligible. When a strong rubber cap is employed, this should be wiped over with a little antiseptic prior to being pierced with the needle of the syringe; the desired dose being abstracted and the needle withdrawn, the puncture hole should be resealed by either melting the paraffin

coating or retouching with the collodion solution. In course of time a negative pressure is induced inside the bottle from the withdrawal of the contents; this has to be relieved by the occasional admission of a few c.c. of air. Here again there is a slight risk of the introduction of sporing organisms, a risk so slight as to be negligible.

The tubing or bottling of the vaccine having been completed, careful workers make a point of confirming the sterility of the finished products by means of the cultural tests described above (p. 36).

It may be noted that the life of rubber caps is naturally very short in hot climates, and that rubber corks are to be preferred under these conditions. The caps are also soon destroyed in any climate if undue heat be employed in remelting the paraffin seal. It is also necessary to mention (1) that all bottles and boxes of ampoules should be carefully labelled and bear the name of the patient, composition of the vaccine, and contained dosages; (2) that bottle or ampoule should be thoroughly shaken before the abstraction of the contents; (3) that vaccines should be kept in a cool dark place.

I will now recapitulate a few of the factors conducive to the production of a vaccine of good immunizing power, minimal toxicity, and low power of exciting local reactions.

(1) Subculture the bacteria as little as possible. Repeated subculturing leads to loss of virulence, which often, but not invariably, is synonymous with loss of immunizing power.

(2) Incubate cultures for as short a period as is consistent with the desired amount of growth. The life of bacteria is often very short; death leads to autolysis and disruption of the cell wall, and to liberation of endotoxin and the production of a toxic vaccine.

(3) Throw down the bacterial contents of the emulsion by aid of the centrifuge, and wash the residual microbes once or twice with salt solution to remove the toxins derived from the surface of the culture medium and from autolysed bacteria.

(4) Avoid undue heating, and indeed heat at all, as a means of securing sterility. Use antiseptic instead, and as little of this as is consistent with sterility. It has been proved for certain bacteria—for instance, the *B. typhosus*—that excess of heat or antiseptic induces a diminished immunizing power and a shortened life for the vaccine.

(5) Avoid the presence of clumps, foreign bodies, and contamination, innocuous as well as noxious. They may be taken as evidence of careless preparation, and usually increase the amount of local irritation. It is sometimes practically impossible to prepare a vaccine of the highest immunizing power and at the same time ensure the exclusion of all spores, in which case it is essential to identify the spores as being those of a perfectly non-pathogenic micro-organism. It may be mentioned that a relatively small number of spores of *B. subtilis* may give rise to considerable pain and redness and even a condition of brawny œdema at the site of inoculation.

(6) Whenever possible, employ a vaccine of such strength that the desired dosage is contained in not more than 1 cubic centimetre of fluid—if in 0.5 c.c., so much the better. The bulk of the inoculum has a decided influence on the amount of local reaction produced.

Combined or Mixed Vaccines.—When first I expressed the conviction, some years ago, that infective conditions by more than one variety of microbe were much more common than they were usually considered to be, and

that many of the symptoms commonly seen in diseases supposedly caused by one particular microbe were in reality to be attributed to the presence of other bacteria existing as a mixed infection, I was ridiculed by many critics. To-day, on the contrary, some of our best authorities doubt if we really know the symptoms set up by a pure infection by such bacteria as *B. influenzæ* and even *B. typhosus*. In other words, they doubt whether a pure infection by such microbes ever occurs, and hold, as Hamer does, that many of the symptoms, say, of typhoid fever, are really attributable to secondary infection by the *B. coli* and *streptococci* of the intestinal tract. The greater my experience the greater is my conviction that one of the chief causes of failure in vaccine treatment is the omission to employ vaccines of sufficient complexity. Bacteria interact upon bacteria in a manner at times almost bewildering. For instance, in liquid cultures the *B. Friedländer* kills off almost any other variety of microbe, no matter what be the initial proportion in their relative numbers. On the other hand, the *B. influenzæ* will hardly grow in the absence of other microbes. Thus, take a plate of almost any solid medium and inseminate it with living *B. influenzæ*. No growth may be visible at the end of twenty-four hours. Now take some more of the same medium, add to it a small quantity of a sterilized growth of pneumococcus or *B. coli* in blood broth, make a plate, and inseminate it in the same way. At the end of twenty-four hours' incubation a growth as profuse as that of *B. coli* may be seen. Thus the pneumococcus toxin favours the growth of *B. influenzæ*, and there is no doubt that *B. influenzæ* greatly increases the pathogenicity of the pneumococcus. Hence in treating a case, say, of bronchial catarrh, where smears show vast numbers of

B. influenzae and relatively very few pneumococci, it is essential to employ a vaccine containing both these microbes. Such a vaccine is known as a **mixed** or **combined** vaccine.

When it is necessary to prepare such a combined vaccine, one of two procedures may be followed :

(1) Each microbe may be isolated, pure cultures secured, vaccines prepared from each, and the several vaccines kept apart or blended in such proportions as may be thought desirable.

(2) The several microbes may be grown together, symbiotically as it is termed, so as to maintain during the preparation of the vaccine those very conditions which obtain at the focus of infection and to preserve the effect of each upon the growth of the others. The vaccine is prepared from the mixed growth and standardized as to content of each variety of microbe. If the proportion is not such as is desired, it may be adjusted by the addition of a pure vaccine of that microbe which is in defect. This method I consider to be the more likely to give a vaccine of the desired immunizing power. At the same time it is not always possible to do this ; for instance, one could not prepare a combined vaccine of *B. coli* and *B. typhosus* in this way, because it would be impossible to differentiate the two microbes when standardizing.

Preparation of Sensitized Vaccines and Their Uses.— Before a microbe introduced into the tissues can excite these tissues to the production of antibodies to that microbe, it is necessary that the bacterial substance be transformed into a soluble state. If the bacillus be alive, it must be killed by the action of bactericidins ; the cell wall must undergo solution, or lysis as it is called, before the contained endotoxin can stimulate the tissues to the

elaboration of anti-endotoxin, and the bacillary protoplasm must be lysinized before it can induce the production of the corresponding antibody. All these changes occur somewhat slowly; it therefore occurred to Besredka that time would be saved if some of these changes were brought about in the bacterial vaccine prior to its introduction into the human tissues. This, he held, could be brought about by treating the bacteria with the corresponding antiserum derived from animals that had been systematically immunized against that particular microbe. This is done by adding to the strong emulsion of bacteria half its volume of undiluted antibacterial serum which has been "inactivated," *i.e.* the contained complement destroyed by heating to 50°–55° C. for 20–30 minutes, maintaining the mixture at incubator temperature for 1–2 hours or at the room temperature for 6–12 hours. The bacilli are then thrown down by centrifugalizing, the antiserum pipetted off, bacilli washed with normal salt solution and again thrown down, and the supernatant liquid removed, this process being repeated till tests show that all traces of serum have been removed.

The bacteria are then emulsified thoroughly with salt solution and standardized. In this, Besredka's original method, the bacilli are not killed, they are simply combined with certain antibodies, as tests upon animals showed Besredka that such microbes were deprived of their pathogenic action and were rapidly phagocytosed. Other workers, in a spirit of disbelief and anxiety to avoid all possible danger, sterilize these "sensitized" vaccines in the usual way, *i.e.* by means of heat or the addition of antiseptic.

The possibility of preparing a "sensitized vaccine" of any particular microbe obviously depends upon the

ability to prepare a suitable antiserum and its availability. Now, it is not possible to prepare a suitable antiserum for all bacteria, so that the number of possible sensitized vaccines is limited. In the second place, although it may be perfectly feasible to produce an antiserum for the bacillus in question, no antiserum capable of sensitizing the particular strain we are dealing with may be available, and to prepare an autogenous antiserum is the work of 3-6 months, so that the opportunity of using a sensitized autogenous vaccine is further limited.

Before attempting to make such a vaccine, it is obviously necessary to test the available antiserum with small quantities of the bacillary emulsion, it being usually assumed that if a serum in high dilution will agglutinate the emulsion, then in the undiluted state it will sensitize the bacteria. This in fact is not the case, the true criterion as to whether a vaccine is sensitized or not being the deprivation of its pathogenic action when tested upon animals, and rapid phagocytosis when tested with leucocytes or tissue cells. The difficulty and expense incurred in securing a suitable sensitizing antiserum, the loss of bacteria involved in the several washings, and the necessary tests upon animals all conduce to making the preparation of a sensitized vaccine an expensive business.

The experiments of Besredka and Broughton Alcock, both on animals and human beings, are held to show that—

- (1) Living sensitized bacteria are perfectly safe to employ.
- (2) They incite the production of antibodies more rapidly and more completely than do unsensitized vaccines.

(3) They produce a higher and more persistent degree of immunity than these.

(4) They are less toxic and therefore less liable to induce severe and undesirable reactions.

(5) Accordingly they are much better adapted for the treatment of acute infections, especially if these be accompanied by a toxic state.

They have not received a very extensive trial in this country, and those who have used them are somewhat divided in their opinions concerning them, and especially as regards the question of their utility in acute infections. Personally I am not persuaded that they possess all the advantages claimed by their originators, but I do believe that they incite a more speedy elaboration of antibodies, and that they are less liable to cause severe reactions. For these reasons I have made it a practice for the past four or five years, whenever it is possible, to add sensitized bacilli to my unsensitized ones, so that the proportion of the former to the latter is as 1:2 or as 2:3. At times I have employed pure sensitized vaccines, especially in acute toxæmic conditions where I have been anxious to get as high a degree of immunity as possible with the least delay and the least risk of exciting an undesirable reaction. Despite a considerable experience, I am not prepared to be dogmatic as to their advantages. I certainly feel safer when using them and able to risk the administration of larger dosages. When advising a patient, I usually put the matter before the patient in that way and leave it to him to decide whether he cares to incur the additional fairly considerable expense.

I cannot shake off the feeling that Besredka's line of thought that led him to evolve the sensitized vaccine was not altogether a sound one. Our object in giving

a vaccine at all is to incite the healthy tissues to elaborate all necessary antibodies to the infecting microbe, *i.e.* bactericidal bodies, lysins, anti-exotoxins, anti-endotoxins, agglutinins, and opsonins. Besredka's aim in employing sensitized vaccines is to save the tissues from part of this work, the part saved being perhaps precisely that part which it is most desirable that we should incite the tissues to perform. Clinical results, as I have said, are not sufficiently definite to enable us to arrive at a just appreciation.

*Gibson's Sensitized Antidysentery Vaccine.*¹—Unsensitized vaccines of killed dysentery bacilli, especially those of the Kruse-Shiga type, cause such intense local reactions as to prohibit their use for immunizing purposes. By sensitizing the bacilli in the ordinary way this toxicity is considerably reduced, but even with small doses a painful indurated swelling is induced, which lasts for about a week. This reaction is too severe to permit the use of even these sensitized vaccines for routine immunization in the army. By means of a modified technique in 1915 I succeeded in producing a sensitized vaccine almost totally devoid of toxicity, but possessing high immunizing powers. I, however, lacked the influence necessary to induce the Army Council to adopt my vaccine, although it was used privately on a few cases in two military hospitals and found to be all I claimed. Graeme Gibson devoted a considerable amount of time and skill to the same question, and claims also to have effected a solution. His line of argument being almost diametrically opposed to that of Besredka and the result being apparently not unsatisfactory, it is possible that the method may be capable of useful extension in other directions, so I consider

¹ *Journal R.A.M.C.*, June 1917, p. 615.

it worth while to give the principles of his technique here and leave the interested reader to refer to the original paper or the forthcoming new edition of *Vaccine Therapy* for fuller details. Gibson argued that the excessive reaction of the unsensitized vaccine was caused by the endotoxin of the bacilli being speedily liberated at the site of inoculation; that inasmuch as the reaction is diminished by sensitizing the vaccine in such a way that anti-endotoxic substances, along with other antibodies, are bound to the bacilli, while he attributes the lack of power in such a vaccine to incite the formation of adequate antibacterial substances as being due to the neutralization of the antigenic powers of the bacilli by the antiserum, it is therefore to be deduced that if the antibacterial substances in the sensitizing serum are removed, while the anti-endotoxin is left, a non-toxic vaccine with adequate powers of stimulating the formation of the necessary bactericidal antibodies will result. He therefore took the antiserum and added a sufficiency of cultures of Shiga's bacillus to remove all the agglutinin from the serum after incubation at 37° C.; the serum so treated was then freed from the bacilli by filtration through a porcelain filter and tested for bactericidins; these were found to have been much reduced in quantity, while the anti-endotoxin was only slightly reduced. The antiserum so treated he calls "absorbed serum."

Rabbits being easily killed by inoculation with a certain dose of a vaccine of Shiga's bacillus, he then tried the effect of giving them a dose greater than this, but administering at the same time a small quantity of this "absorbed serum." He not only found they survived, but on testing their blood after two doses had been given, found a high development therein of agglutinins,

of bactericidal substances, and of antitoxin. He then tested the effects upon man, and found that 0·1 cubic centimetres of absorbed serum given along with 500 millions of Shiga's bacillus retained sufficient of its anti-endotoxin to neutralize the toxins contained in this amount of vaccine, with the result that their simultaneous administration induced a local reaction of quite moderate intensity which passes away within forty-eight hours. A second dose of 1,000 million bacilli mixed with 0·2 c.c. of absorbed serum was given seven days later, the reaction produced being about the same. Tests upon the blood ten days after the second dose showed that a good production of agglutinin and of antitoxin had been induced. Gibson therefore advises that this sero-vaccine be employed to produce immunity against dysentery in the following way. A first dose, consisting of 500 millions of each of Shiga's bacillus, Flexner's bacillus, and Bacillus "Y" mixed with 0·1 c.c. of his absorbed serum, is to be followed after seven days by a dose containing twice those amounts of each of the bacilli and of absorbed serum. It remains for clinical experience to pass its verdict on the value of this sero-vaccine ; if the verdict be favourable, it remains perhaps for bacteriologists to utilize the principles in the production of similar sero-vaccines in the case of other bacteria, vaccines of which are apt to induce severe local and general reactions.

CHAPTER IV

THE ADMINISTRATION OF THE VACCINE, ITS EFFECTS AND RESULTS AND THEIR USE, IN CONTROL OF DOSAGE AND INTERVALS

The **syringe** is by no means a negligible factor in the administration of the vaccine, especially in these days, when many of the best-known English makes are faulty in the extreme. I have paid anything from 6s. to 36s. for my 1 c.c. syringes, yet only about one in three has been satisfactory. The commonest fault is that the syringes are not even water-tight; it is little use standardizing a vaccine with the utmost care if a quite unknown amount is going to be lost, either through a faulty junction of barrel and metallic junction to carry the needle, or through the needle not fitting the syringe perfectly. I buy my needles in dozen boxes made by the makers of the syringe, but rarely find six that fit the syringe perfectly. Another common bad feature of present-day syringes is the fitting of the needle into its head; the two are not made in one part, but the former is luted into the latter and usually either insecurely, or some of the luteing partly occludes the opening of the needle. The very best syringe on the market is the fused quartz one, supplied by Allen & Hanbury's, but it costs at least 30s. My favourite syringe is the all-glass one made by Luer in all sizes from 1 c.c. to 50 c.c. It is always beautifully made, being absolutely air-tight.

The only objection to it is the extreme ease with which the hard glass of which it is made fractures ; it will not stand dropping from a very low height, nor any great sudden changes of temperature. It should therefore be sterilized either by always keeping it in a mixture of one part ether to three parts absolute alcohol to which sufficient lysol or carbolic acid is added to make a 3 per cent. solution, or by placing it in cold distilled water (tap water deposits lime salts, which interfere with the delicate working of the syringe), gradually raising it to the boil, and maintaining it at that temperature for two to three minutes. Never drop it into hot water. My advice therefore is, buy two really good all-glass 1 c.c. syringes, graduated preferably in twentieths of a c.c. (Burroughs & Wellcome used to supply a very nice one of this type), test them carefully at the time of purchase—they should be absolutely air-tight—and take every care of them. At the same time buy several dozen needles of the Schimmel type, and test every one of them with alcohol or ether: fill the syringe, occlude the opening of the needle with two fingers, compress the fluid, and see if there is a leak. Leave nothing to guesswork or the assurance of the salesman, and you will be saved much of the annoyance I have suffered. The needles should not be too fragile, long, or slender, nor yet too coarse, but needles which will readily pierce a thick skin without bending ; they should not have a speck of rust, and the points should be well bevelled and sharp. Needles should be sterilized by boiling in absolute alcohol and washed out with absolute alcohol when done with, dried, vaselined, and the wire threaded through them ; every now and again they should be polished with watchmaker's sandpaper, number 00, and the tips refreshed on the oilstone.

Believe me, these warnings are not unnecessary, and patients fully appreciate a doctor who uses good needles.

The instrument, having been sterilized, should be put together with sterile forceps, and the desired dosage aspirated therein, either from the well-shaken ampoule or bottle.

Route of Inoculation.—As with the administration of most medicaments, vaccines may be given by various routes: (a) into the subcutaneous or muscle tissues, (b) intravenously, (c) orally, (d) per rectum. The oral and rectal routes may both be dismissed as having proved quite unsatisfactory. Absorption from stomach, bowel, or rectum is an uncertain quantity, and in addition the secretions have a destructive action upon all proteids and toxins, and these constitute that part of the bacillary substance which is of value in the production of immunity.

Whether the vaccine is introduced into the subcutaneous tissues or the muscles matters little from the point of view of resultant immunity. Absorption of the inoculum is slower from the subcutaneous tissues, but the effect of the inoculation is as a rule less painful than when the muscles are utilized; nevertheless the muscles of the arm or buttock are quite suitable for the purpose.

The intravenous route has not been much employed; probably the fear of septicæmia resulting from any possible contamination or virulent microbes left unkilled has had much to do with this. So far as it has been employed it has been found very suitable. Local reaction is much minimized, but the general reaction is increased to such a degree that diminished dosage is advisable. A few observations tend to show that the production of antibodies resulting from a dosage only one-quarter of that used via the subcutaneous tissues

is approximately the same. This must not be assumed to have been proven, and further experiments are much to be desired, as some observations cast doubt on the specificity of the antibodies formed in this way.

Site of Subcutaneous Inoculation.—This again is a small matter, but of no little concern to the patient. If a male, the areas available are to be preferred in this order: upper arm just below the insertion of the deltoid, buttock a couple of inches below the iliac crest and 2-3 inches from the sacro-iliac joint, abdominal wall just external to the linea alba. In females there is less choice, especially if they are inclined to resent an area being reddened which will be exposed in evening dress; with them the order is: upper arm between the shoulders, $1\frac{1}{2}$ -2 inches below the centre of the clavicle. There is one site particularly to be avoided if the patient be very fat, and that is the buttock. In this case the inoculum will lie in adipose tissue and be absorbed very slowly, with just a possibility of auto-infection occurring at the site. This actually occurred in a certain case where I was retained as expert for the defence. The inoculum did not consist of a vaccine, but of a mixture of adrenalin and pituitary extract: 3 inches of fat lay over the muscles; the highly vaso-constrictor fluid failed to absorb, auto-infection by the *B. coli* ensued, and the patient died of septicæmia.

I can quite imagine the same thing occurring, especially if the dose of vaccine happened to be a large one. As nothing would be noticed for a few days, and there would be no vaccine available for testing, if that which was used had been contained in an ampoule, it would be quite impossible to prove that the vaccine was sterile and that the accident was due to auto-infection, as I was able to prove for a certainty in the above case, and

the doctor would receive the whole of the blame, or at least share it with the maker of the vaccine.

The selected area should be well rubbed with anti-septic solution, a good fold of skin and underlying subcutaneous tissues taken up firmly between left thumb and forefinger, the needle plunged boldly and quickly in to the depth of about an inch, the tissues released and inoculum slowly expressed from the syringe. Just as patients hate a needle that is rusty, even to a microscopic degree, or that possesses a dull or bent point, so they dislike having the needle pushed in slowly; they like it done as if the doctor meant to do it. Readers would hardly believe the number of comments patients have made to me as to the careless ways in which they have been inoculated—and of dislike at “finnicky” methods. Use good tools and get it over and done with as quickly as possible.

The operation over, the puncture may be touched with the weak antiseptic or dried and a little collodion applied.

Mishaps Possible in Inoculation.—(1) Commonest of all is the pricking of a small vein, and the consequent production of a slight hæmatoma. This is far less common than one would expect, but is sufficiently common to make one always consider the question of site of inoculation, especially in women, for if it does happen it is sure to occur in the case of a woman who has to appear in evening dress. Pressure with the finger-tip over the site of inoculation the instant the needle is withdrawn tends both to diminish the risk of hæmatoma and to limit it if it should occur. Once it has occurred, nothing can be done beyond warning the patient to expect an unsightly bruise for some time to come.

(2) *Pricking of a Nerve.*—This is a very much less

frequent accident, but I have twice seen mild cases of wrist-drop so produced. The pain may be somewhat severe if the vaccine be injected into the nerve-sheath. It may last for a few hours, and the resultant paralysis for a few days or even longer.

(3) *Abscess Formation.*—This should practically never occur with a properly prepared vaccine, but with very high dosages in small bulk the possibility of slow absorption and auto-infection from the overlying skin must be admitted. The doctor, however, is sure to receive the blame for lack of care and maladministration.

The Effects of Inoculation.—These are to be divided into (1) *local*, (2) *focal*, (3) *general or constitutional*.

(1) A **local** reaction of varying degree and duration is inevitable in the great majority of instances. Rarely nothing is to be seen or felt; commonly within 8-12 hours there appears a slight swelling with redness, tenderness, and some pain.

These should pass away completely within 24-48 hours. Occasionally the reaction is a severe one, this being the more common when high dosages of the more toxic vaccines are employed, as in antiplague, antidysentery, antityphoid, and anticholera inoculations. The presence of spores of such non-pathogenic air organisms as *B. subtilis* in the vaccine tends to produce the same effect. An area of brawny œdema of greater or less extent may be produced, the tissues may become very red, hot, and painful, and such glands as the axillary may become swollen and tender to the touch. Compresses of hot water, of crushed ice, or of the two alternately usually afford relief, but I have seen morphia rendered necessary.

(2) **Focal Effects.**—These are usually evidenced within twelve hours by a slight exacerbation of the conditions

and signs obtaining at the focus or foci of infection and of the patient's symptoms. A boil, for instance, may get slightly larger and feel more hot and tender. A suppurating wound may discharge more freely and areas of repair look redder and more vascular and exude serum. An infected area in the lung will be detected more readily with the aid of the stethoscope ; signs will be heard over a wider area and become moister in character and dry crackling râles will be transformed partly into moist or even bubbling ones. All these changes are indicative of increased blood supply to the infected parts : usually they begin to retrogress between the eighteenth and thirty-sixth hours, and should have disappeared six to twelve hours later. Occasionally the cycle of changes is delayed by as much as twenty-four hours.

(3) General or Constitutional Effects.—These are partly due to the contents of the vaccine itself, partly to the responses made by the healthy tissues locally and generally, and partly to the changes brought about at the foci of disease. Usually they begin to be felt within six hours, occasionally not before the twenty-fourth hour, and rarely not before the forty-eighth hour. The temperature may be raised a fraction of a degree or even several degrees, the pulse accelerated or slowed, respirations hurried or slowed ; occasionally shivering fits, rigors, and fainting may be induced. The skin may feel cold and clammy or hot and moist.

There may be a feeling of malaise of very varying degree, mental depression, headaches, burning feeling in the eyeballs, nausea, sickness, and vomiting. There may be definite diarrhœa or constipation ; skin rashes of varying kinds and degrees may result, from a slight general erythema or urticaria to a rash resembling that

of measles or scarlet fever. One patient described to me a rash like that of scarlet fever, but very dusky and sometimes almost black. Unfortunately I never had a chance of seeing it. Very rarely there may be a slight general œdema. These rashes may be followed after a day or two by a general irritating dermatitis, which may also occur independently of any rash.

A general reaction amounting to slight feeling of malaise or headache, described to me by one patient as "a feeling of having been inoculated," with rise of temperature of not more than 2° F. at the most and slight acceleration of the pulse, I never regard as being indicative, especially in cases of lung disease, of anything more than a desirable response of the healthy tissues to the vaccine. Anything more than this necessitates a careful consideration of the cause, with the view of determining whether the dosage was excessive. Severe or peculiar reactions, such as some of those detailed above, are usually due to some personal idiosyncrasy or excessive susceptibility to the vaccine, and may necessitate a careful general overhaul of the patient. If they occur with a first inoculation, a very considerable reduction should be made in the second dose, the administration of which should be deferred for at least seven days after the passing away of all signs of the reaction.

Occasionally information of great value is afforded by the occurrence of some peculiar general reaction, as in the following case. A hard-riding north-country squire, who had always led an outdoor life of great activity, had pneumonia of moderate intensity of the right base two winters in succession. The following autumn he came to me for a course of preventive inoculation. When I had reached a dose of 250 millions he complained of feeling very faint twenty-one hours after the inocula-

tion. I repeated the dose with the same result, so on the next occasion **again** gave him 250 millions and saw him at the twenty-first hour. I found the heart thumping hard, and not only working at high pressure but also irregularly and even intermitting. There was thus no doubt that the two attacks of pneumonia had left their mark on the heart musculature, and I was able to warn him accordingly. We went on with the inoculations, and for the past two years he has escaped even a slight cold, and I am glad to say also the recent epidemic of influenza.

When to Inoculate.—We have seen that the period of greatest response to the vaccine lies between the sixth and eighteenth hours, which may be regarded as the period of lowered resistance. It is a very good thing if this period can be passed in bed; this can easily be brought about by doing all inoculations in the afternoon and early evening. In this way the focal and general reactions, which we have incited to a degree only that is desirable in the interests of our patient, pass unnoticed during the hours of sleep.

Occasionally it is highly desirable, especially in the case of lung infections, that the changes we have induced should be carefully observed. This again can be easily achieved by doing the inoculation either early in the morning or very late at night, when the patient has retired to bed. With experience of vaccine work in general and of a patient in particular, it soon becomes easy to predict when any reaction will be at its height, and thus to adjust the hour of inoculation if it be desirable to observe the precise effects produced by any given dosage.

The Results of Inoculation.—We have seen that the aim of vaccine treatment is to incite the elaboration by

healthy tissues of the various antibodies which are inimical to bacterial growth, among these antibodies being (1) antitoxins, which neutralize the endotoxins and exotoxins formed by the bacteria and render them innocuous ; (2) bactericidins, which cause the death of the microbes ; (3) lysins, which have the power of dissolving their cell walls and so of facilitating the neutralization of their endotoxins ; (4) opsonins, which render the bacterial protoplasm more palatable to the phagocytes ; (5) agglutinins, which cause the collection of the bacteria into clumps, and so perhaps facilitate their phagocytosis. As a result of careful laboratory tests conducted upon the blood of animals and men infected by various pathogenic bacteria, it has been shown that the increased elaboration of some or all of these bodies is conducive to the extinction of the infection and recovery of the patient ; this being so, it obviously becomes advantageous to know whether a similar production of antibodies can be induced by artificial immunization with the aid of vaccines, and it has been found that such is the case.

For instance, the immunization of healthy animals with killed or living cultures of the various microbes leads to the elaboration of such high amounts of the corresponding antitoxins, bactericidins, lysins, etc., that the sera of these animals are frequently employed therapeutically to produce a passive immunity in cases of disease ; for instance, antidysenteric serum is largely used in cases of bacillary dysentery, its high antitoxic content being of value to neutralize the endotoxins of the dysentery bacillus ; similarly the value of anti-diphtheritic serum is well known in cases of diphtheria. The production of these antisera is usually a slow and difficult business, extending over 3-12 months ; if

vaccine treatment is to be of any avail in acute infections, it is necessary to know whether the formation of the various antibodies can be achieved with the necessary rapidity.

The various reactions, local, focal, and constitutional, are all indicative of the response of the tissues to the inoculation, but unfortunately do not afford a measure of the antibodies formed ; the estimation of most of these is too difficult and tedious a process to become available for use in clinical medicine. Wright accordingly devised a method of measuring one of these antibodies, *viz.* the opsonin, assuming that the amount of opsonin in the blood was some measure of the various other antibodies and of the immunizing response of the tissues. Such doubts have, however, been cast in recent years both upon the accuracy of the method of measurement and upon its value as a guide to the patient's immunity, that this somewhat difficult and costly estimation is now rarely employed as a therapeutic guide, it being held that the focal and general reactions and clinical condition of the patient form a sufficiently reliable guide in vaccine treatment. A sufficient number of careful estimations of the various antibodies formed in response to the introduction of vaccines into the healthy tissues has, however, been made to establish the fact that the use of vaccines does lead to a very rapid response in the production of antibodies, and that by careful adjustment of dosages and intervals between the administration it is frequently possible to bring about a cumulative effect in this direction. Unfortunately several factors militate against the possibility of achievement of the desired result, *i.e.* the extinction of the infection. Among these may be mentioned : (a) that while our vaccine does lead to the production of certain

antibodies, it may fail to influence the speedy production of others which are essential to recovery ; (b) that even if adequate amounts of the necessary antibodies are formed by the tissues, it may yet be impossible for them to reach the focus of infection. The blood and lymph supply to the part may from various causes be too limited to carry thither anything approaching an adequate amount of antibodies. For instance, in cerebro-spinal meningitis the meningococcus performs its deadly work in the spinal and cerebral spaces, which are almost entirely cut off from all communication with the blood and lymph streams ; it matters little therefore what may be the amount of antibodies in these latter, as they are not carried thence to the cerebro-spinal fluid. This question of accessibility of the infected areas to the various antibodies is one of the utmost importance, yet one which is so frequently neglected that it becomes one of the most common causes of failure in vaccine treatment. The doctor should ask himself this question in every case, " Have the antibodies of which I am bringing about the elaboration free access to the infected areas ? If not, what can I do to promote this ? "

Whatever leads to increased blood and lymph supply to the part also leads to the access of the antibodies, hence warmth, massage, passive congestion induced by Bier's method, removal of layers of coagulated blood, fibrin, lymph, and fibrous tissue by application of peroxide of hydrogen, solutions of the hypochlorites and perhaps by scraping, the induction of increased permeability of the parts by application of citrated salt solution, are some of the means which may be taken to bring about an increased flow of the antibodies.

Control of Dosage and Intervals.—We have thus acquired this amount of knowledge : (i) that by the

use of appropriate vaccines it is possible to incite the rapid formation by healthy tissue of one or more of such various antibodies as antitoxins, lysins, opsonins, bactericidins, and agglutinins ; (2) that by taking suitable measures it is sometimes possible to bring about the access to infected foci of these antibodies ; (3) that while the measurement of the amounts of the various antibodies circulating in the blood is too difficult and laborious a process to be available as a routine guide to the process of immunization, the tissues evidence their definite response to the stimulus by means of **reactions**, local, focal, and general in nature.

Now, inasmuch as the production of antisera with a high content of antibodies is proved to be dependent, among other things, upon the dosages employed and the interspacing of the doses, and it has been repeatedly shown—experimentally, as for instance by Gordon and Horder and by Hine, in the case of the meningococcus—that small repeated dosages are more toxic than a single dose of an equal or greater aggregate, and that the latter leads to a much more rapid and high production of antibodies, it is obvious that the same factors will come into play in vaccine treatment, and it is necessary to ascertain whether it is possible, in default of suitable laboratory tests, to utilize the various reactions as a guidance to the best dosages and intervals. This I strongly hold to be the case. Other bacteriologists, on the other hand, take exception to the use of such dosages as will give rise to a reaction other than a local one. These must necessarily conduct a course of vaccine treatment on purely empirical lines, their only guidance being the past experience of themselves and of others, and the clinical condition of the patient, both in my judgment very unreliable guides.

I hold that every case undergoing vaccine treatment is a "law unto itself," and that the production of mild and carefully controlled focal and general reactions is an essential, not only as a guide to dosage and intervals, but even for the production of an immunizing response. In other words, "no focal or general reaction, no elaboration of antibodies, or at least an elaboration of an amount insufficient for the needs of the case." One might just as well give digitalis in a case of heart disease in amounts which have no influence upon the rate and volume of the pulse. Little wonder that the results of vaccine treatment are often unsatisfactory to patient and doctor.

A perusal of the list on pp. 53, 54, imperfect though it probably be, of what constitute focal and general reactions—for the amount of local reaction at the site of inoculation I consider to be little or no measure of immunizing response—will doubtless induce my readers to say, "Well, I should be very sorry to bring about reactions like these in any of my patients," and this remark would be well justified. In all things there is a happy mean. There is a degree of reaction which is highly desirable, and a degree of reaction which is highly undesirable. Our aim, therefore, is to produce reactions of the former kind, and to achieve this requires skill, care, experience, and careful clinical observation. Let us therefore arrive at a conception of what kind of reaction is to be desired. As regards the **focal** reaction: this of course cannot always be observed, as for instance in cases of septicæmia. Fortunately in such cases the deficiency is nearly always more than counterbalanced by the production of a general reaction unmistakable in kind and import. On the other hand, the focal reaction can very often be watched and estimated with very great

accuracy: the best instances of this kind are afforded in cases of pulmonary disease (for several good examples of this, showing the extreme value of the focal reaction as a guide to immunization in respiratory troubles, see my *Bacterial Diseases of Respiration*, Chaps. VII and X, pp. 92, 157, and also the charts on pp. 132-8 of this book).

We will suppose we have a case of chronic pneumococcal infection of the right lower lobe, which, lying dormant all the rest of the year, lights up into activity at the beginning of each winter. A very careful clinical examination in August reveals nothing more than an area as big as a half-crown, of very slightly impaired resonance, the centre lying, say, $1\frac{1}{2}$ inches external to the nipple in the fifth or sixth space. The stethoscope reveals possibly slight diminution of air entry and of vocal resonance, and a few crackles or an occasional click midway through respiration or at the end of a deep inspiration, which may be only elicited by means of a cough and sharp deep breath; there may be no sputum at all, or a trace in the morning in which are a few pneumococci, perhaps accompanied by a few *B. influenzae*. I have needled several such areas when no sputum was obtainable, introduced 2 or 3 c.c. of broth, applied suction after a few seconds, and inseminated culture media with the few drops of fluid so obtained, and secured free growths of organisms. This is one of the commonest of all medical conditions, and is, in my opinion, responsible for by far the greater proportion, even perhaps 80 per cent., of all cases of adult pneumonias. Let us now give what I call a diagnostic dose of pneumococcal vaccine, say 250-500 millions, at 9 a.m. Between noon and 3 p.m. the patient will notice a few slight coughs, and that he is bringing up a little sputum. Two or three hours later he may feel a little out of sorts,

have a slight headache, and perhaps a slight pain over the right lower chest. He is also coughing and spitting a little more freely. If now we examine the chest we find no difficulty in hearing râles. Over an area perhaps 3 to 4 inches square, or an area following the course of the ribs, and in two interspaces, usually the fifth and sixth or sixth and seventh, we hear a number of dry crackling and some moist râles, and perhaps a long rhonchus between the middle and end of inspiration, or towards the end of expiration. Rarely slight friction is to be made out. This focal reaction is usually at its height between the sixth and fifteenth hours. In the case mentioned on p. 55 it happened with clockwork regularity at the twenty-first hour. A few hours later the action begins to subside, and between the twenty-fourth and forty-eighth hours the "status quo ante" should be re-established. This is a perfect example of a focal reaction of a nature and degree just such as is to be desired if vaccine treatment is to benefit the patient.

In infections of the eye, pharynx, larynx, and superficial structures generally, these focal reactions can be easily watched, and it may be stated that a focal reaction which begins between the sixth and twelfth hours, results in a slight exacerbation of the symptoms present, reaches a maximum between the twelfth and eighteenth hours, and retrogresses completely within twenty-four to thirty-six hours, going on thereafter to clinical improvement, is a focal reaction that can result in nothing but benefit to the patient.

It is, however, when we encounter the general or constitutional reaction that the specialist takes alarm and the general practitioner feels at sea, yet surely it must be evident to the meanest intellect that a dose of vaccine which produces no obvious effect upon the

patient will probably also be insufficient in amount to be productive of the greatest good. As I have said, to endeavour to bring about benefit with the aid of a vaccine without the production of any constitutional change in the patient visible to the careful clinical scrutiny of the doctor, is like giving digitalis in a case of heart disease and expecting the patient to benefit when no effect is produced upon the pulse.

But again there is moderation in all things. A general reaction may be of a kind and degree which is highly desirable or highly undesirable. No doctor desires a patient to have rigors, to faint, to be covered with urticaria, or to be kept up all night with diarrhoea ; what he does desire is that the tissues of the patient shall evidence their efforts to produce antibodies in one or more of the following ways : (1) by a slight rise in temperature of not less than 0.5° F. and not more than 1.5° F., which subsides completely within twenty-four hours ; (2) by a slightly accelerated pulse, ten to twenty beats per minute over the patient's normal. Both these signs are indicative of bacterial toxin, liberated either from the bacteria contained in the vaccine or from those which have been killed off and lysinized at the focus of infection, acting in the former case upon the thermo-genetic centre, in the latter upon the heart's musculature. If an excessive reaction of either kind be produced, it is indicative either of excessive dosage or, in the latter case, of the fact that the heart muscle has already been seriously impaired by the long-continued action of the toxin of the bacterial infection, and is a danger-signal to which due heed must be paid.

Slight feeling of malaise, lassitude, or slight headache, passing off well within twenty-four hours, are evidences of a general reaction of a not undesirable degree.

Any reactions greater than the above are to be considered as not being excessive and undesirable only in cases in which preventive inoculation against typhoid, fever, cholera, plague, etc., is being carried out with high dosages of vaccine. There is something strangely illogical about the minds which can accept these excessive reactions as not being undesirable in these cases and as being indicative of the active formation of antibodies, and yet will deny the advisability of producing the much milder type of general reaction which I have advocated above.

One type of general reaction remains to be mentioned, *viz.* that in which the patient makes steady clinical progress without any other obvious sign of immunizing response.

Hypersensitiveness or Hypersusceptibility.—This is a very rare condition. In all my experience of thousands of cases I have met with only one case. Clinical experience in the use of vaccines is now very considerable, and suitable initial dosages for practically all the pathogenic bacteria are reasonably well known. In cases of hypersensitiveness marked intolerance of the customary initial dosage is displayed by a resultant general and focal reaction of a degree altogether undesirable. These cases cannot be distinguished beforehand in any way. My case was one of chronic pneumococcal infection of both lower lobes, presenting the features I have described on p. 62. He had been ill for two years, had passed the last six months in a sanatorium, and looked in perfect health. I gave him a dose of 25 millions of a stock pneumococcal vaccine. He reacted violently, focally and generally. Ten days later I gave 25 millions of an autogenous pneumococcal vaccine; to this he reacted with rigors, severe sweating, malaise, diarrhoea, and

wasting. I at once suspected the condition and waited a month before giving 5 millions ; this he tolerated badly, so next time I gave him 500,000, to which he reacted nicely. After several doses of this I tried a sensitized autogenous vaccine ; this not being a conspicuous success, I tried a stock sensitized vaccine. After many months of treatment I was able to raise the dose to 10 millions, but to this day 7 millions suits him best and 15 are quite excessive. Seven millions keep him fit and well, and able to do his very exacting work, and for two years he has escaped from his previously frequent colds. If he omits treatment for a fortnight, he at once begins to relapse and feels quite "out of sorts."

We have thus arrived at the decision that a dosage of vaccine which produces a focal or general reaction such as I have described, which begins to subside between the eighteenth and twenty-fourth hours, and has completely subsided between the twenty-fourth and forty-eighth hours, is a dosage well calculated to bring about a further good response in the matter of production of antibodies.

So long as any given dosage produces such a reaction, it should be maintained at that level, and not be increased. Only when the patient ceases to make such a response, and only then in the event of the clinical progress not continuing to be satisfactory, should such increase of dosage be resorted to. These increases are usually made to the extent of a 50 to 100 per cent. increase on the preceding dosage.

It is quite impossible for me to find words sufficiently strong to condemn the procedure followed by so many, more especially in tubercular therapy but also when using vaccines, of plotting out a scheme of dosage at

the beginning of the course and making increments of dosages at prearranged dates, absolutely irrespective and independent of the clinical response which the patient is making to the vaccine. Therein lies one of the commonest, if not actually the commonest, causes of disappointment and failure in vaccine therapy.

Interval between Doses.—Experience derived in the preparation of various antisera from animals teaches that the tissues respond satisfactorily when the interval between low doses is maintained at seven to ten days. This conclusion was also arrived at when opsonic index estimations were employed to control dosages and intervals in the treatment of chronic infections of human beings. This interval is also one satisfactory, as a rule, to patients, and accordingly is the one usually adopted, though I must confess without scientific reasons that are altogether satisfying. To put it in a slightly different and perhaps more accurate way: without adequate proof that this interval is one adapted to all patients, suited to all cases of chronic bacterial infection, or best calculated to ensure the maximum formation of antibodies, but in order partly to satisfy the requirements of patients, dosages are usually so adjusted in cases of chronic bacterial infection that reinoculation may be performed after the lapse of seven to ten days. We have really no proof, clinical or otherwise, that smaller dosages given at intervals of three or five days or that larger dosages given at fortnightly intervals would not be preferable in many instances. For prophylactic inoculations the advisability of lengthening the period between the inoculations to over fourteen days is strongly indicated by the careful experimental observations of Dreyer and others (*Lancet*, 1918, April 6th, p. 498). They find that an interval of three

weeks leads to the production of the maximum amount of antibodies, and certain American workers have arrived at the same conclusion.

For my own part, giving as I do dosages that secure these mild focal and general reactions, considered undesirable by some workers who employ as a routine the seven-days interval, I yet sometimes feel that I should do better if I shortened the interval to five days ; I am, however, restrained by the consideration, which is undoubtedly sound, that it is better to employ too long intervals rather than too short ones, and too small dosages rather than too big ones. In either case the former alternative can do no active damage, whereas the latter certainly may. Hence in cases of chronic infection let the doctor by all means employ an interval of seven to ten days, controlled however by clinical observation and modified whenever necessary to suit the responses of the case.

Cases of **acute** infection stand upon a totally different footing : in the first place, they will only tolerate a greatly reduced dosage as compared with chronic cases ; in the second, if a seven-days interval were employed it would usually mean that the first dose must kill or cure. It thus comes about that authorities who shirk using the control of focal and general reactions in chronic cases yet resort to such control in acute cases. A small initial dose, say of 5 million streptococci, is given, and the effect upon temperature, pulse, and clinical condition recorded at intervals of three to four hours. If no effect is produced, the dose is repeated or increased, perhaps to double, on the following day, and so on. If a reaction of any sort is produced, viz. clinical improvement, slight rise of temperature followed in a few hours by fall, acceleration of pulse followed by retardation,

one usually awaits the first definite sign of retrogression, and then repeats that dosage.

Sooner or later, as a rule, the dosage in question seems to lose its power of exciting an adequate immunizing response, when it is increased by 50-100 per cent. As the patient improves, if he does improve, it is often assumed that higher dosages will be better tolerated; these are accordingly given, and the interval increased by one to two days. Thus in cases of severe acute infections, small doses are usually given at intervals of one or two days; as progress is made, the interval is extended to three days, and perhaps later to four or five days.

Personally, when a patient is doing well clinically, I always remember the French proverb "Le mieux est l'ennemi du bien" and leave well alone, maintaining both dosage and interval at the level which brought about improvement until clear evidence is forthcoming that an increased dosage would be beneficial. I am more inclined to push dosage when cases are doing badly than when they are doing well.

CHAPTER V

PROPHYLACTIC OR PREVENTIVE INOCULATION

SINCE the admission among vaccines of preparations of emulsions of living bacteria, as for instance Besredka's sensitized vaccines, Castellani's typhoid vaccine, and Strong's plague vaccine, ordinary inoculation against smallpox may fairly claim to be regarded as the first instance of prophylactic vaccine treatment, despite the fact that not only does it alone among vaccines induce immunity by the actual production of a disease, but that as now practised it achieves this by the communication of the disease in a modified form. As originally practised by the Turks, the virus employed was of direct human origin, and the actual disease was induced. Now a virus of human origin is modified by passage through a calf, and in this way the virulence is considerably reduced. The technique of ordinary vaccination is so well known to all medical men as not to require description.

The distrust of the procedure present in the minds of so many of the public should finally be entirely removed upon the publication of the results of vaccination as seen in our army during the recent war, and especially in that portion operating in Serbia and adjacent countries, where the disease is at all times rampant to such an extent that in times of peace yearly vaccination was a frequent practice.

Prophylactic inoculation is such a simple matter and is conducted on such stereotyped lines that I have thought it wise to describe it before dealing with **therapeutic immunization**, or the employment of vaccines in the combat of actual disease.

Prophylactic inoculation has in recent years made great strides and been extended to the prevention of many diseases, as will be seen from the following list of infections, arranged in the order in which I will consider them:

- (1) Typhoid and paratyphoid fevers.
- (2) Cholera.
- (3) Plague.
- (4) Malta fever.
- (5) Dysentery.
- (6) Nasal, tracheal, and bronchial catarrhs and pneumonia.
- (7) Whooping cough.
- (8) Rabies.
- (9) Anthrax.
- (10) Scarlet fever.
- (11) Infections by *B. coli*.
- (12) Hay fever.

(1) **Antityphoid Inoculation.**—The evolution of antityphoid vaccination has been a gradual one, the amount of research that has been done enormous, and the literature relating to it would alone fill many large volumes. Limitations of space compel me to pass over much that is of interest, insert only what is material, and describe the final evolution of the procedure. A very brief reference to the history of the subject is, however, pardonable, as the lesson to be learnt therefrom is of practically universal application and importance in vaccine therapy. After the Boer War the attempt was

made to assess the results achieved by the preventive inoculation of the troops engaged therein, and a furious battle ensued between Sir Almroth Wright and Professor Karl Pearson, the famous statistician. When I ventured to point out that neither had any accurate facts upon which to found an argument, giving as my reason the firm conviction that infections by the paratyphoid organisms, against which no attempt had been made to establish immunity, were very much more prevalent than was commonly believed, I was laughed to scorn. Subsequent events have shown how true my observation was. Fully convinced of its accuracy, I immediately advocated the use of a combined vaccine of the *B. typhosus*, paratyphosus A and B. This was the second combined vaccine to be used, my combined for colds being the first. As evidence accumulated, Castellani and other bacteriologists endorsed my views and upheld my procedure, yet, incredible as it may seem, the Army Councils of practically all the combatant nations during the great war decreed that a vaccine of the *B. typhosus* alone should be employed. The result was well seen in the Dardanelles Expedition. I have the full statistics of practically the only hospital in Egypt where thorough methodical examinations of every case were made. The records of all the others, many or most of which will assuredly pass into print and be assumed to be accurate, are not worth the paper they are written on. The records I speak of establish the fact that infection by the *B. typhosus* was practically unknown, the paratyphoid fevers comprising well over 90 per cent. of all the cases ; fortunately the virulence of these organisms, the paratyphosus A and B, is much lower than that of the *B. typhosus*, or thousands of lives would have been thrown away by this insensate

piece of folly and ignorance. As it was, thousands of men were rendered for months unfit for military service when they could least be spared. Later, the combined vaccine was universally adopted, with the immediate result that paratyphoid fevers also received their quietus.

It may be thought that I am making overmuch of this and belabouring my steed unduly, but if there is one thing I wish to impress upon the mind of my readers it is this, that whether in prophylaxis or treatment, absolute accuracy of the infective organism or organisms is a prime essential, and one should always be on the watch for mixed infections. It may perhaps impress it on the mind more clearly if I mention here that what has been proved in the case of so-called typhoid fever has been found to be equally true in the case of other acute infectious diseases: thus there is not only a *Vibrio cholerae*, but also one or more *V. paracolerae*; not only one *B. dysenteriae*, but several; not only one *M. micrococcus melitensis*, but probably two; and not even one *Spironema pallidum* in syphilis, but probably two; and about a dozen different known types of pneumococcus and of streptococcus; while I have long known that there are several varieties of the *B. influenzae*. If, therefore, it is proposed to establish immunity against any particular disease, care must be taken to use a vaccine upon which complete reliance can be placed; if it be proposed to treat a case of any disease with a stock vaccine, the same holds true; and if with an autogenous one, then a thoroughly competent bacteriologist, fully awake to the frequency with which mixed infections occur, should be furnished with proper specimens or preferably be given full facilities to take his own.

There have been many attempts made to elaborate

an ideal antityphoid vaccine, *i.e.* one which, while inducing a maximal production of antibodies against the *B. typhosus* and its allies, at the same time gives rise to reactions, local and constitutional, of such a mild type that no interference is occasioned with the performance of his necessary duties by the soldier or workman. Thus in addition to the ordinary vaccine of the English and American army authorities and of most vaccine laboratories, we have the sensitized vaccines of Besredka and Broughton Alcock, the autolysed vaccine of Vincent which is little more than a solution of the endotoxins, the living but heat-attenuated vaccine of Castellani and others. These possess little if any advantages over one prepared from specially selected strains of low virulence and of proved high powers of inciting the production of the various antibodies, of which the sterility is secured solely by the addition of 0.5 per cent. carbolic acid or 0.3 per cent. tricresol, or by heating for half an hour to 53° C.

If heat be altogether avoided, it is found that the vaccine is slightly less toxic and certainly preserves its immunizing powers unimpaired for a longer period ; such a vaccine kept in a cool dark place should suffer no deterioration in six months and very little at the end of twelve or even twenty-four months.

The technique of antityphoid inoculation differs in no way from that described on p. 52. The authorities in different countries have adopted slightly different methods of immunization : when time is an important factor, as in the face of a threatened outbreak or of an army urgently needed to take the field, reliance is usually placed upon two inoculations at an interval of ten days, the first dose consisting of 1,000 millions *B. typhosus* and 750 millions of each of *B. paratyphosus*

A and B, the second of double these amounts; when the inoculations can be spread over a longer period, the initial dose may be 500 millions of each of the three organisms, the second of 1,000 millions B. typhosus and 750 millions paratyphosus A and B, and the third of double this last amount; in accordance with Dreyer's observations the interval between the doses being made as near three weeks as possible. At the German Medical Congress held at Warsaw in May 1916, the enhanced protection afforded by at least three doses of the vaccine as observed upon the German army was clearly brought out. Of the three organisms contained in the combined vaccine the paratyphosus B is the most toxic, the paratyphosus A the least, and it is the presence of the former of these which has occasioned the greatest difficulty in so arranging dosage as to secure adequate immunity and at the same time confine the reaction within moderate bounds. Very careful study of the resultant production of the various antibodies in man and animals has clearly established these very important points:

(1) The dangers of the negative phase or period of lowered resistance are practically non-existent.

(2) Accordingly the presence of a threatening epidemic or recent exposure to infection is no contraindication to prophylactic treatment, but rather the reverse.

(3) The immunity, resulting from the simultaneous use of the vaccines of three or even more organisms, against each microbe employed is at least as good as if it had been produced by the use of a vaccine containing one only of the several constituents; indeed some observations even tend to show that the degree of immunity obtained is enhanced by the procedure.

(4) The saving of time resulting from the use of combined vaccines is very considerable.

(5) There appears to be no increase in the degree of local and general reactions, and accordingly no need exists for the employment of reduced dosages.

(6) The more nearly the period between inoculations can be approximated to between eighteen and twenty-one days, the higher the antibody formation.

(7) The resultant immunity falls very slowly, and maintains itself at an adequate level for about twelve months ; at the same time the case-mortality in the German army was only 2·3 per cent. among those who had been inoculated within six months, whereas it was even over 6 per cent. among those who had been inoculated within twelve months but not within six months.

The various antibodies have been detected in man in increased amounts six and even ten years after inoculation.

(8) Vaccination against smallpox can be performed upon one arm and antityphoid inoculation upon the other arm at the same time without danger to the patient or unduly upsetting him, the one procedure having no ill effect upon the other.

Castellani (*British Medical Journal*, 1917, September 15th, p. 356) has made a further advance by the introduction of his **tetravaccines** and his **pentavaccines**. The former contains not only the *B. typhosus* and paratyphoids A and B, but also the *Micrococcus melitensis* or *Vibrio cholerae*, and is styled accordingly Vaccine T.A.B.M. or T.A.B.C.

His **pentavaccine** is one of the **tetravaccines** with the further addition of the *Bacillus pestis* of plague, and is dubbed Vaccine T.A.B.M.P. or T.A.B.C.P. He claims

that the reactions they induce are only of moderate severity, and that the resultant immunity against each of the bacteria is quite satisfactory. In twenty-six cases he has used a **hexavaccine**, Vaccine T.A.B.C.P.M., and states that even with this the reaction is less than with Haffkine's monoplague vaccine. With each of these vaccines the initial dosages are as follows in millions: *B. typhosus*, 500; *Para A* and *B*, 250; *B. pestis*, 500; *V. cholerae* and *M. melitensis*, 2,000. The second dose is double the first.

Effects of Antityphoid Inoculation. (1) **Local.**—Tenderness begins to make itself felt in five to six hours, and is at its worst in about eighteen hours, when redness may have developed over an area of 2 inches radius around the site of inoculation. Occasionally the lines of the lymphatics may be traced, and some tenderness of the corresponding lymphatic glands may result. The day after inoculation the arm should permit of free use, and all signs should have disappeared at the end of forty-eight hours.

(2) **General or Constitutional.**—Some degree of malaise begins in about six hours. In a small percentage of cases there is a tendency to faintness; occasionally a rigor may come on within six hours; rarely there is diarrhoea, vertigo, or a slight diffuse erythema; and after the lapse of two or three days urticaria or a general irritative dermatitis.

There is usually some headache and a slight degree of pyrexia. Only occasionally does the temperature rise to 101° F., and rarely to 103° F. This usually subsides within eighteen to twenty-four hours.

Very rarely indeed hyperpyrexia and delirium have been noticed, although mental depression is fairly common. This description of the local and constitu-

tional effects of antityphoid inoculation apply equally well to all the prophylactic inoculations.

Contra-indications.—These are very few indeed. Alcoholics as a body react more strongly than others, and sometimes to such a degree that abstention from all forms of alcohol for at least twenty-four hours prior and subsequent to inoculation is advisable in every case. Cases of nephritis certainly excrete toxins slowly, and the presence of kidney disease must be taken as necessitating greater caution in the procedure. It has been recorded that old cases of trench fever have after inoculation shown return or increase of albumen in the urine, and in a few instances a return of pain in the shins and other symptoms, as if the trench fever had been awakened into activity. A slight risk of awakening dormant foci of tuberculous infection has been mentioned to me, but I have never seen such an occurrence myself.

Anticholera Inoculation.—This, like antityphoid inoculation, has received much more attention during the war, and its value been amply demonstrated. How chaotic was the knowledge in 1915 may be gathered from this anecdote. I was rung up by an important individual at the War Office and asked if I could supply anticholera vaccine for use in the Dardanelles. On replying that I was fortunately in possession of a number of recently isolated strains from Russia, where it had been rife among the Russians and Austrians, I was asked what dosage I could supply. I replied any dosages they desired. The answer to this was that someone had advised the use of half a million, and someone else of 1,000 millions—they did not know what to use. I then said that, in my opinion, any initial dosage of less than 500 millions was useless for prophylactic purposes,

and that half a million might just as well be put down the sink. Accordingly I supplied 500 millions for the first dose, 1,000 millions for the second, and 2,000 millions for the third. I was only able to ascertain the effect in a few cases—these all escaped cholera, and told me that the local and general reactions caused them even less inconvenience than their antityphoid inoculations. This vaccine was prepared from agar cultures of recently isolated, very highly virulent strains, and was killed—a perhaps quite unnecessary procedure—by heating at 53° C. for twenty minutes. I say “a perhaps quite unnecessary procedure” because it has been well established that the living cholera vibrio when implanted in the subcutaneous tissues is incapable of doing harm.

If three doses can be given, I think 500, 1,000, 2,000 millions at intervals of not less than fourteen days are quite satisfactory; if there is time for two only to be administered, then 1,000 millions and 2,000 millions should be given. If the interval between doses can be extended to three weeks, so much the better. Kolle's procedure is to give a first dose of 2 milligrams of an agar culture emulsified in 1 c.c. of saline and sterilized at 53°–55° C.; the second dose given a week later in double amount. If only one dose can be given, this is 3–4 mgm. I presume the weight is that of the moist microbes; if it were of the dried, his initial dose would be about 20,000 million vibrios; 2 milligrams of the moist probably correspond to about 1,000 millions.

The results were discussed at the German Medical Congress at Warsaw in May 1916. The consensus of opinion was distinctly favourable, but there was considerable difference of opinion as to the probable duration of the resultant immunity. This was held to reach a maximum in about fourteen days. Kolle considered

the protection lasted for at least twelve months, others said they found a considerable fall in the antibodies after six months. In the Austrian army reinoculation after three months was practised if there was any imminent danger of infection. It was found that when inoculation was practised during the course of an epidemic, the number of new cases suddenly fell five to eight days after the first inoculation.

In the Austrian army the case mortality among the uninoculated varied from 40-60 per cent., among the inoculated it was sometimes very low indeed, and never rose above 20 per cent.

The following figures for the Greek Army during the Balkan War of 1912-13 are of distinct interest—though I cannot say the nature of the vaccine nor dosage employed.

	Percentage of men attacked.	Case mortality per cent.
Among the uninoculated	9.29	27.5
Among those inoculated once	4.25	12.2
,, „ „ twice	0.7	10.2

The utility of anticholera inoculation and the value of repeated doses would appear to have been well established from the experience in these three armies; not only is the incidence rate markedly lowered, but there is, contrary to the view previously held, a definite reduction in the percentage case mortality.

The recent discovery that the *Vibrio cholerae* is not the bacteriological entity it has always been held to be, but that, like the *B. typhosus*, it has three closely related congeners known as *Paracholera bacilli*, points to the necessity of employing a polyvalent vaccine for immunizing purposes. When attention has been paid to this point, even more satisfactory results may be anticipated.

Antiplague Inoculation.—It is a cause for thankfulness that the recent war has shed very little additional light upon the value of antiplague inoculation. Its good results were, however, sufficiently well established prior to 1914.

The two best-known vaccines for the purpose are those of Haffkine and of Strong. The former prepares his vaccine by growing cultures for four to six weeks at a temperature between 27° C. and 30° C. in flasks of broth to which a little oil has been added, the flasks being shaken from time to time to throw down the stalactites of growing bacilli. He takes great pains to ensure sterility by heating to 65° C. for one hour, and then adding 0.5 per cent. carbolic acid. The first dose is 3 c.c. for a man, 2.0–2.5 c.c. for a woman, and smaller doses for children; a second dose may be given ten to fourteen days later of only one-third the magnitude of the first. Both liability to infection and case mortality are considerably reduced, and Haffkine states that if an inoculated European contracts the disease he always recovers. Absolute immunity is held to be ensured for three months, and relative immunity for a very much longer period. The presence of an epidemic is no contraindication to inoculation, indeed Haffkine states that if a person already infected and incubating the disease be inoculated, the disease may even be aborted. Strong at Manilla employs cultures of living attenuated bacilli, claims to have had no ill effects, and to have reduced the mortality rate at least fourfold. It may be recalled that Castellani's pentavaccine contains plague bacilli among the others.

Anti-Malta Fever Inoculation.—The elucidation of the ætiology of Malta fever and the precautions and hygienic measures adopted in view of this have pro-

duced such a marked influence on the incidence rate that the disease promises to be stamped out by these means alone. I am not in possession of any recent reliable information on the subject of preventive inoculation. An initial dose of 1,000 millions can be safely followed seven days later by one of double this amount ; quite possibly an initial dose of 2,000 millions would be free from objection, this being repeated or even increased to 5,000 millions fourteen to twenty-one days subsequently. As with the *B. typhosus* and *V. cholerae*, so the discovery has been made of closely allied variants of the *M. melitensis* necessitating the use of a polyvalent vaccine for prophylactic use. Castellani's tetra- and pentavaccine contains this microbe in initial doses of 500 millions.

Antidysentery Inoculation.—As I have already mentioned, great difficulty has been experienced by bacteriologists in evolving an antidysentery vaccine of good immunizing power, owing to the great toxicity of vaccines of the Kruse-Shiga type and the consequent inability to administer the vaccine in adequate dosages. I have also already pointed out (p. 45) that Graeme Gibson and myself, by different methods, succeeded in overcoming this difficulty completely, and it is now just as easy to prepare a reliable sufficiently non-toxic polyvalent antidysentery vaccine as it is to prepare an antityphoid one. Broughton Alcock also claims success, his method being to prepare in the ordinary way a sterilized, standardized emulsion of the bacilli. To every 2 c.c. of this emulsion, 10 c.c. of heated normal horse serum or 20 c.c. of heated human serum are added, and the mixture allowed to stand overnight at room temperature or in the ice-chest. The bacilli are then thrown down by centrifugalising, well washed with

normal saline, again thrown down, and then sufficient normal saline added to bring the strength to 350 mill. per c.c. The initial dose is 1 c.c., distributed over four different places in the back; after eight or nine days a second dose of 2 c.c. is given, and a third later if possible.

The procedure with Gibson's vaccine has been already fully described on p. 47, that with my own being similar. Two doses are essential, three to be preferred, at intervals of fourteen to twenty-one days. Animal experiments would seem to prove fully the value of the treatment. As regards my own vaccine, it has only been used prophylactically in a few private cases; not one of them complained of the reaction, and not one contracted the disease, though exposed freely to infection; the number of my cases is, however, far too few to afford much evidence. Graeme Gibson (*Journal R.A.M.C.*, May 1918, p. 476) has had better opportunities for testing the value of his, but he admits that his control cases were not entirely satisfactory as controls; the tests were conducted on men both in the Near East and on the Western front; in each case it would appear that the incidence rate was very materially diminished among those prophylactically treated. He comes to the following conclusions:

(1) That while the use of his vaccine produces no period of lowered resistance, it is more difficult to raise the immunity with the dysentery bacilli than it is with other organisms of the intestinal group.

(2) That a period of about twenty-one days after the second dose has to elapse before the full production of antibodies is reached.

(3) That when possible three doses should be given.

(4) That the resulting immunity lasts probably for four to six months.

(5) That prophylactic treatment is advisable among bodies of men: (a) at the beginning of the summer when dysentery has previously been endemic, or when carriers of the disease are suspected to be present; (b) when an epidemic threatens to occur.

To this I would add that in private practice it can confidently be recommended to patients who are about to proceed on a visit of a few weeks' or months' duration to districts where bacillary dysentery is common at that time of year.

Anticatarrhal Inoculation.—The value of an efficient method of immunization against the infective agents in acute bacterial diseases of the respiratory system will be fully appreciated by all after the experiences with the world-wide epidemics of 1918-19.

As all who are familiar with the history of contemporaneous medicine are well aware, I was the first to apply vaccine treatment both to the treatment and prophylaxis of respiratory diseases. This was over fourteen years ago, and during the whole of the subsequent years I have been a close student of the bacteriology of every epidemic, have had ample opportunities of applying prophylactic measures, and of assessing the value of the procedure. As the result of this experience I have no hesitation in expressing the opinion that prophylactic inoculation against bacterial invasions of the respiratory tract can be made one of the most successful procedures in the whole domain of medicine. I advisedly say *can* be made, for many misconceptions exist and much bad advice has recently been given through lack of clinical knowledge and ignorance of the essential principles involved, as I will show in the following pages.

In my extensive studies I have always preserved a

perfectly open mind as regards all the questions that have arisen and have made trial of widely divergent schemes of dosages on ample clinical material, and being a practising physician have had every opportunity of observing the results obtained over a long period of years. I therefore claim to be an unbiassed, experienced, and trustworthy guide in this matter. Important as is the question of composition of the ideal vaccine, the question of appropriate dosages is vastly more important, presents the greatest difficulties, and is accordingly the one concerning which the greatest mistakes have been and are being made.

To deal with these in order, the list of bacteria capable of setting up acute catarrhal infections of the respiratory tract, either alone or, as is much more commonly the case, in association with other members of the group, is an extensive one, but the following is a complete one in the present state of our knowledge : (1) *B. influenzæ* ; (2) *B.* of Friedländer ; (3) *B. proteus* ; (4) *B. typhosus* and its allies ; (5) *B. septus* ; (6) *B.* of Hoffmann ; (7) *Pneumococcus* ; (8) *Streptococcus* ; (9) *M. catarrhalis* ; (10) *M. paratetragenus* ; and (11) probably a coccoid facultatively anaerobic filter passer.

Of these the *B. proteus* and the *B. typhosus* group are very rare, and only secondarily involve the respiratory tract from some other focus of infection.

If the reader will refer to the statistics of each epidemic given in my *Bacterial Diseases of Respiration*, he will see how markedly these microbes appear in cycles. For instance, the *B. septus* may be found in 80 to 90 per cent. of the cases in each epidemic for two or three successive years, and then disappear altogether for four or five years. I have not seen a single case of respiratory catarrh, acute or chronic, set up by Friedländer's bacillus,

B. septus, or *Micrococcus paratetragenus* for years ; cases due to Hoffmann's bacillus have been very few indeed ; and for the past three years *micrococcus catarrhalis* seems to have largely lost its virulence. On the other hand, B. *influenzæ*, *pneumococcus*, and *streptococcus* have been, and still are, rampant and of very high virulence. Now, this is a very important point when we come to consider the composition to be adopted for our prophylactic vaccine. The reader may ask, " What earthly objection is there to incorporating them all, especially when you have just been to such pains to point out that an antityphoid vaccine must contain three different microbes, and that Castellani has added two more to these in his pentavaccine, and you state moreover that it has been proved that the body is capable of elaborating antibodies to all these in undiminished amounts at the same time ? " Now, this is all perfectly true, and I know I lay myself open to the charge of inconsistency when I oppose this procedure. As we shall see, I advocate the use of very considerable dosages of the necessary organisms, and it is well to keep down the bulk of the inoculum as much as possible. If adequate dosages of the essential organisms are to be contained in a suitable bulk of diluting fluid, great technical difficulties will be encountered if at the same time we introduce adequate dosages of unessential organisms. I am moreover a great believer in the happy mean, and feel that the present state of our knowledge does not justify us calling upon the tissues to elaborate an unlimited number and quantity of antibodies without good reason. No indications whatever at present exist of the likelihood of the B. of Friedländer or *M. paratetragenus* suddenly assuming virulence and initiating fresh catarrhal epidemics ; the vaccine should always be reasonably fresh,

and ample warning would be given and the opportunity afforded us of incorporating these microbes in our vaccine should this prove desirable.

It may therefore be assumed that to meet all immediate needs our prophylactic anticitarrhal vaccine for **general** use should contain only (1) *B. influenzae*, (2) *pneumococcus*, (3) *streptococcus*, (4) *M. catarrhalis*. Furthermore, if instead of a vaccine for **general** use we have to consider one for special **individual** use, a careful clinical study of past catarrhal attacks in that particular individual may enable us, in the manner I have described in *Bacterial Diseases of Respiration*, to determine definitely that this person is not susceptible to one or more of these remaining four microbes, and already possesses ample immunity against them. This may be regarded as a somewhat unnecessary refinement, and it must be confessed is not altogether devoid of risk, even in the hands of those who have made a special study of this question and are able with considerable accuracy to diagnose the infective agent from a careful, detailed description of the clinical symptoms, for not every patient is able to give his clinical history with the desired accuracy. However, I have adopted this procedure with considerable success in a very large number of cases.

Let us assume then that for at least the next twelve months we are going to employ a vaccine of these four microbes. It then remains for us to ensure that all the prevalent strains of each of these is duly represented in the vaccine. Of the *B. influenzae* there are unquestionably two types, varying considerably in morphology and cultural characteristics. At present I am not able to supply details for their differentiation, and this difficulty is best overcome by making this vaccine highly

polyvalent ; not less than eight strains should be employed and twelve are to be preferred. As regards the pneumococcus, we know that at least ten different types exist in different parts of the world. One or two of these appear to be peculiar to and predominant in South Africa ; one or two of the remainder appear to be peculiar to and predominant in the United States ; the same holding true for other types in England, France, and other parts of the world. A few of the types appear to be represented in every country. These various types can be fairly clearly differentiated the one from the other by serological and other tests. From this it is very clear that it is essential to incorporate in our vaccine each and all of the types prevalent in the country in which the inoculated person is about to reside. It is no use to inoculate a soldier about to serve in France or South Africa with the types prevalent in England and omit those prevalent in France or South Africa respectively.

What is true for the pneumococcus also holds, but even to a greater degree, for the streptococcus. I have been very much struck by the various types of streptococci found in the sufferers from the epidemics of 1918-19, and am convinced that far too little attention is being paid, especially to the non-hæmolysing strains. They have not only presented great morphological variations, but also marked cultural differences, even upon the ordinary media. If, however, we substitute for these latter a medium composed of 2 per cent. agar, 2 per cent. glucose, and 2 per cent. dextrose, and add sufficient citrated **human** blood to tint it deeply, the cultural differences become much more pronounced, and while it has been no uncommon thing to find three or even four different varieties of streptococci present

in the secretions or post-mortem material, one variety has occurred with great frequency, especially in the cases presenting the graver clinical symptoms. This variety I believe to be closely related to, if not identical with, the enterococcus of Thiercelin. Its inclusion is essential for the preparation of a satisfactory vaccine, and the other prevalent types should be adequately represented.

Numerous variants of the *M. catarrhalis* also exist, and as a rule three or four distinct types are to be found during each epidemic.

To sum up, if a satisfactory prophylactic vaccine is to be prepared, it is essential that due regard be paid to the inclusion of such strains of each microbe as are (1) peculiar to the locality in which the inoculated person will reside; (2) represented during any prevalent epidemic. At least a dozen strains of each microbe should be employed whenever this is possible. Such a vaccine is to be found in my "Combined Vaccine for Colds,"¹ and in its slightly modified form my "Prophylactic Influenza Vaccine."¹

We will now consider the question of dosages to be employed, and, as I have said, much misapprehension exists and many erroneous ideas are held with regard to this matter. How these have arisen it is not easy to discover. The very men who would not for a moment question the absolute necessity of employing full and adequate dosages of the various microbes to ensure immunity against the typhoid fevers, Malta fever, or cholera, yet totally ignore the vast accumulated experience of others, and without being able to give any satisfactory reasons, advocate the use of the most absurdly small

¹ Obtainable from W. Martindale, 10, New Cavendish Street, London, W.

dosages of *B. influenzae*, pneumococcus, streptococcus and *M. catarrhalis*. In the very early days of vaccine therapy the statement was made by somebody that *B. influenzae* vaccine was toxic, and this statement was swallowed and digested by others. As a matter of fact I know of no vaccine which is less toxic. I have given dosages of 5,000 millions over and over again, and have never seen the slightest ill-effect result, except possibly in one case, and here the evidence is far from conclusive. Some now endeavour to excuse their old custom of giving low dosages by stating that the scanty growths obtained from media ill-suited to the growth of the bacillus are far more toxic than the free growths obtained from the more suitable media now employed. This is a pure assumption, an assumption moreover inconsistent with facts. I have over and over again given similar high dosages of the two vaccines as prepared on the different media, and find no difference whatever; the two are equally atoxic. Others endeavour to justify their low dosages by claiming wonderful antigenic properties for the vaccines as they prepare them. These claims again are not justified by facts. There is no method known of raising artificially the antigenic value of the *B. influenzae*; all that can be done is to isolate the microbe as speedily as possible and prepare the vaccine from first subcultures, the method I have always advocated and always used. The only common catarrhal organisms whose antigenic value is capable of being influenced are the pneumococcus and streptococcus, and steps are sometimes taken in this direction. The vaccines as prepared by some of the most strenuous advocates of low dosages are sterilized by means of heat, one of the best methods of lowering their antigenic value; in mine heat is never used to ensure sterility, so that the antigenic value of

a given dosage can scarcely fail to be higher than that of the same dosage of my opponents as regards dosage. It may also be mentioned that no reliable experimental method exists for testing the antigenic value of a heated vaccine ; this can only be learnt from its clinical results. Finally, it may be added that none of the advocates of low dosages are able to produce any statistics of their results which will bear scrutiny or criticism, nor any experimental evidence of the adequate immunizing effect of such dosages. On the other hand, I have had fourteen years' clinical experience of anticitarrhal inoculation, and have been induced steadily year by year to increase my dosages. I now obtain, and for several years past have obtained, highly satisfactory results in very large numbers of cases, and Wynn, Matthews, and others entirely uphold my views, even if they have not yet advanced quite so far on the path of high dosages ; the research work of Avery, Chickering, Cole, and Dochez at the Rockefeller Institute,¹ and of Lister in South Africa,² clearly demonstrates the perfect safety of high dosages of the pneumococcus, even of much higher ones than those I advocate, and of the necessity for their use if adequate immunity is to be secured in the very susceptible races they have studied.

What is true of the *B. influenzæ* and pneumococcus is also true of the streptococcus and *M. catarrhalis*, and I am very strongly indeed inclined to take the view that, while marked differences in the immunizing values of different strains of any given bacillus certainly exist, given sufficiently polyvalent mixtures of the various

¹ *Journal of Experimental Medicine*, 1915, XXI. p. 114, etc., etc.

² Publications Nos. 2 and 8 of the S. African Institute for Medical Research.

pathogenic **aerobic** bacteria, equal weights of the bacterial protoplasm of the several kinds of microbes will produce approximately the same degrees of immunity. On p. 35 I have given the numbers of certain microbes contained in 1 milligramme of their substance. We know from clinical experience that an initial dosage of 500 millions and a total dosage of 4,000 millions of *B. typhosus* will give very satisfactory immunity ; from this I believe we can at least approximately calculate the appropriate initial and total dosages of any other microbe against which we desire to secure immunity, as for instance of the *B. influenzae*, *pneumococcus* and *streptococcus* : the figures thus arrived at correspond by no means badly with those I advocate as the result of clinical experience.

Before coming to a final conclusion as to the appropriate dosages for our prophylactic catarrhal vaccine, one point needs consideration, and this is a point of the very highest importance to which no other worker but myself has paid the least attention. When we speak of prophylactic inoculation we presuppose that the tissues of the patient are free from infection by the microbe or microbes we are about to inject. Once tissues have become infected by a microbe, their whole nature as regards that microbe **has** undergone a complete change. They have become **sensitized** to that particular bacterial proteid, and respond to the stimulus its introduction affords to a much more marked degree, and probably in a different manner, as compared with healthy normal tissues.

If the respiratory system be already infected, therefore, by any of the catarrhal organisms, the tissues generally are sensitized to that particular bacterial proteid, and may respond much more actively to the

corresponding vaccine. Before subjecting anyone, therefore, to prophylactic inoculation, it is advisable to assure oneself that the tissues are healthy, and not already grossly infected by one or more of the microbes contained in the vaccine. As I point out on p. 62, foci of infection by the pneumococcus exist in the lower lobes of the lungs of very many individuals, the *B. influenzæ* being fairly often associated with the pneumococcus and the streptococcus, and less frequently **with the *M. catarrhalis***. This more or less dormant infection is in my opinion one of the commonest, and at the same time one of the most important, of all medical diseases, being responsible for by far the greatest proportion of all sporadic cases of pneumonia in adults. These, when **their foci light up into activity**, hand on the infection to others, thereby initiating such epidemics as that of 1918. The pneumococci in these foci very frequently belong to a different type from that which the "carrier" carries in his mouth, and to this fact is partly due the failure of the American workers to assign them their proper place in the ætiology of pneumonia, both sporadic and epidemic. To the waking into activity of these dormant foci many acute attacks of respiratory catarrh are due; in the dormant state they cause much chronic ill-health and frequently manifest their presence by mild cardiac and circulatory disturbances, by dilated stomach and chronic indigestion, by myalgias, and by such nerve troubles as sciatica and herpes zoster. Quite apart from the bearing it may have on the question of dosage for prophylactic inoculation, **this infection is therefore one** the detection of which is of great importance to the patient. The position of these foci is remarkably constant, and a history of repeated colds in any individual, especially if accompanied by any of the symptoms detailed above,

should excite a suspicion of their existence. With a little practice their detection is the work of a very few minutes or even seconds, but full deep breathing by the patient and post-tussic auscultation is an essential.

Should such a focus be detected, the case becomes one rather for treatment than for prophylaxis, and for this see Chapter VIII; but should a course of treatment not be practicable and prophylaxis be desired, a reduced scheme of dosage, certainly as regards the pneumococcus and possibly as regards the *B. influenzæ*, is advisable. Occasionally these cases do react strongly to moderate dosages of vaccine, and it is just possible that the erroneous idea regarding the toxicity of *B. influenzæ* vaccine may have arisen through the effect produced in an undiscovered case of this kind. With practice the detection of these foci is such an easy matter that no difficulty should be allowed to present itself and be considered as adequate excuse for failure to examine the chests, even in the case of large bodies of men who have to be inoculated. One medical officer conversant with the work could examine men in the army almost as speedily as another could give the inoculation.

The accumulated evidence, experimental and clinical, already briefly given regarding the other prophylactic vaccines has left no doubt in our minds that, whenever possible, at least **three** doses should be given to secure adequate immunity, that **four** and even **five** are preferable to three, and that the interval between doses should not be less than fourteen days and may preferably be eighteen to twenty-one days. At the same time clinical experience has shown that very good immunity is secured when the seven-days' interval is employed.

Assuming that three doses are all that are possible,

our **minimal** scheme of dosages for an adult **healthy** man or woman would be as follows :

Millions of	B. influenzae.	Pneumococcus.	Streptococcus.	M. catarrhalis.
1st dose	500	250	250	250
2nd dose	1,000	500	500	500
3rd dose	2,000	1,000	1,000	1,000

In addition, it is well if to these a further dosage be added of sensitized B. influenzae, pneumococcus, and streptococcus, to the extent of half those indicated above, as thereby any resulting reaction may be minimized and a high degree of immunity be more speedily secured.

If a fourth dose is possible, this may contain double the dosage of the third dose, if no excessive general reaction was produced thereby ; if a severe reaction did result from the third dose, then this should be repeated. Alternatively to the above would be a scheme making the first dose to contain the quantities indicated above for the second, and the second and third to contain the quantities indicated above for the third.

If only two doses are possible, then the first should be the above second, and the new second the above third.

If, however, the presence of a focus has been detected and, a therapeutic course being out of the question, prophylaxis is desired, a lower scheme of dosage must be employed, and if large bodies of men are to receive inoculations and prior examination of the chests is an impossibility—though only the strongest possible exigencies can, in my opinion, justify such an excuse and such a procedure—it may be considered advisable to adopt for these also this lower scheme of dosage. Among healthy trained bodies of men the percentage with foci should be so small as to justify the greatest good for

the greatest number, and the risk being taken of severe reactions in this small percentage, in which case the scheme already given should be followed.

The new initial dosages will be as follows: *B. influenzæ* 200 millions, *pneumococcus*, *streptococcus*, and *M. catarrhalis* 100 millions.

In these "focal" cases the inoculation should be given in the morning, the recipient remaining quiet all day, in order that the temperature may be taken in the evening and chest examined. If no marked reaction occurs in any way, the second dose may be the same as that already given **in the above table**; but if there be a marked reaction, inoculation should be deferred till the fourteenth day if possible, the second dose **then** being *B. influenzæ* 500 millions, *pneumococcus*, *streptococcus*, and *M. catarrhalis* 250 millions. The third dose, again, will depend upon the nature of the reaction. If this be mild, the dosage may be increased to double, the interval being made as nearly fourteen days as possible; if, however, the reaction is again a severe one, reinoculation must be deferred till the fourteenth day, and no increase of dosage should be made.

If further prophylaxis be possible, the nature of the reaction to this third dose must decide whether any increase is permissible in the dose given after another fourteen days.

For **children** under three years of age the initial dosage may be taken as one-fifth of that for a healthy man, for those between three and seven years one-quarter, between seven and ten years one-third, and from ten to sixteen years one-half of that for a healthy man.

In healthy people the **resultant reactions** should not be so severe as to interfere in any way with the patient's usual mode of life, and should entirely pass off within

twenty-four hours, with the possible exception of slight local tenderness and swelling. The period of lowered resistance is also comprised within twelve hours, so that patients should be inoculated in the late afternoon or evening, preferably of a Saturday, so that the period of greatest lowered resistance may be passed safely in bed, and, needless to say, the patient should not spend the evening in a theatre or music-hall. No alcohol should be taken for twenty-four hours prior to and following the inoculation.

The resultant immunity from a course such as I have described should remain at a high level for at least six months ; the best time, therefore, to begin treatment is some time between the middle of September and middle of October, so that a high degree of immunity is established before the onset of the cold weather and persists over the time when winter colds are most rife.

As in the case of antityphoid and anticholera inoculations, the appearance of an epidemic at any other time of the year should be the signal to the highly susceptible that a course of preventive inoculation had better be begun.

My experience of the results extending over the past twelve years, during the first seven or eight of which I employed dosages too small to bring about the best results, leads me to the firm conviction that in anti-catarrhal inoculation with my Combined Vaccine for Colds we possess one of the most potent weapons in therapeutics for the control of any epidemic disease. Universal success is of course not to be anticipated, for the following reasons : (1) Some persons seem to be so extraordinarily susceptible to any and all of the catarrhal organisms that it may prove an impossible task to raise their immunity to a sufficiently high level ; (2) a microbe

may become epidemic which is not contained at all in the vaccine at that time ; (3) a strain of any given microbe may become epidemic not represented in the vaccine ; (4) the existence already of foci of infection such as I have described may have escaped the doctor's notice ; until these foci are eradicated—a most difficult result to achieve—the infected individual will always remain especially liable to auto-infection of other parts of the respiratory tract and to the local extension of the foci of infection. A complete measure of success may be anticipated in those who have undergone a full course of treatment with adequate dosages, such as those I have given, to an extent varying from 60 to 80 per cent. in different years. In 15 to 20 per cent. of the remainder, moderate success is achieved, in that both the number and severity of such attacks as they do occur should be minimized ; in the remaining cases, little or no benefit seems to accrue for some reason of which I can offer no explanation. I have had through my hands many cases that have given a history of not being able to remember the time when they were free from a cold, being rapidly cured by means of an autogenous vaccine, and remaining well ever since, the routine being to have four or five doses twice yearly, beginning treatment in the February and September of each year.

I may mention the interesting fact that not one single case of mine that undergoes such methodical prophylaxis or one which had completed a full course of treatment during 1918 incurred an attack from the severe epidemic that raged during that year. The explanation of this may partly depend upon the fact that I, being fully awake to the imminence of such an epidemic, had devoted especial care both to the preparation of a vaccine in which all the prevailing strains of the

several microbes were fully represented and to the advisability of employing a fuller scheme of dosages than any I had utilized in previous years. My results were so extraordinarily good that I forebore from making any attempt to record them in the medical journals, lest doubts should be cast upon my veracity. The recent announcements by several workers of their successes and the urgent necessity for placing the dosages to be used in the prophylaxis of respiratory disorders on a surer foundation now emboldens me to record my results during the past year.

I have myself immunized and supplied the necessary dosages for the immunizing of a total of 180 cases. Of these not a single case incurred the prevailing epidemic, and two only had slight colds in the head which did not even necessitate a single day's stay in the house. This series is very closely paralleled by the results of the inoculation of 247 of the staff of the New Zealand Stationary Hospital in France by Captain Armitage during the severe epidemic of pneumonia during 1918. The composition of his vaccine and the dosages employed were very similar to mine—not a single case that he inoculated incurred the disease.

Some of the results obtained by other workers are as follows: At Westmeath Asylum Dr. Gavin inoculated some of the staff; for various reasons the others could not be done. Of the inoculated 3 per cent. only were attacked in a mild form; of the uninoculated 80 per cent. were stricken down. Dr. W. H. Wynn (*Lancet*, 1918, December 28th, p. 874) records that at one institution 112 nurses and ward maids received two inoculations and 53 were not inoculated. Of the 112, two only subsequently had mild attacks; of the 53, 25 had mild attacks in June and escaped in the later epidemic, 1 had a mild attack in

February and subsequently very severe bronchopneumonia, 14 escaped in the earlier part of the epidemic but contracted influenza later on, 2 with severe bronchopneumonia, and 1 dying. The figures are not strictly comparable, as the same periods are not covered in all cases, the outbreak among the 14 last mentioned preceding the inoculations indeed being the occasion for the inoculation of the remainder. Even if these be excluded—a hardly necessary proceeding—the effect of the inoculations prophylactically is sufficiently convincing.

Antipneumonia Inoculation.—Whilst strictly anti-pneumonia inoculation forms an integral part of anti-catarrhal inoculation in general, and has to a certain extent already received consideration in the preceding section, in view of the special attention attracted to this particular branch of the subject by the epidemics of 1918-19 it is perhaps advisable to consider it in a little fuller detail.

As I have already pointed out, it is my firm conviction, induced by close observation of the clinical histories of a considerable number of such patients over a term of years, that sporadic pneumonia in the adult is due almost entirely to the awakening into activity of the pneumococci lying dormant, often for many years, at such foci in the lower lobes of the lungs as I have already described. I have pointed out also that the type of the pneumococci recoverable by lung puncture of the foci does not necessarily correspond with the type which these same individuals may constantly harbour in their mouths. Having given rise to a pneumonic attack in their host, these pneumococci are dispersed into the air by fits of coughing and in the sputum, infect other individuals, gain increased virulence by passage, and

initiate such epidemics as that of 1918. If adequate measures were taken to stamp out these foci in the carriers, or, in the event of failure to achieve this difficult task, pneumonic attacks prevented by prophylactic inoculation of the host, epidemic pneumonia and pneumonic catarrhs and bronchitis would become rarities. Unfortunately it has been left to myself to discover the existence of these foci, and medical men, bacteriologists and clinicians alike, are at present ignorant, not only that they do exist, but also that they exist in such a relatively considerable percentage of the population.

The whole history of bacteriological research hardly contains a finer example of the value of properly directed and painstaking research than that afforded by the efforts of Avery, Dochez, Chickering Cole, and others of the Rockefeller Institute¹ and of Lister in S. Africa to elaborate an antipneumonic vaccine and a serum of universal applicability.

The results of these two independent sets of workers have been to establish the facts that—

- (1) The pneumococcus group comprises a considerable number of closely allied members, which by means of suitable antisera and other methods can be differentiated from each other.
- (2) A strain endemic or epidemic in one locality may differ markedly in certain directions from that of another locality, where indeed it may not even be represented.
- (3) Usually more than one strain or type is represented in a given locality, though as a rule one type predominates.
- (4) The immune bodies of one type may be entirely without influence upon the members of another type.

¹ Monographs of the Rockefeller Institute for Medical Research, No. 7, October 16th, 1917, etc.

(5) An efficient vaccine must contain each and all of the strains or types peculiar to the locality in which it is going to be employed.

(6) The dosage necessary to produce high immunity differs with different races and with different individuals of the same race, but is in all cases far in excess of that commonly employed.

(7) These high dosages can be used with perfect safety and produce no ill-effects.

Lister claims to have demonstrated in the rabbit that intravenous inoculation of the vaccine gives rise to a much greater production of agglutinins and opsonins than does the subcutaneous route, and also that the serum of a man inoculated intravenously on three occasions with a relatively weak vaccine, viz. 100 millions, made from several strains was proved to contain agglutinins and opsonins for each of these strains. I have always considered that the formation of antibodies was almost certain to be lower when the intravenous route was adopted, but in view of these observations of Lister and the experiments of Gibson with the intravenous route in antidyseptic inoculation, feel that further researches are highly desirable, and that they may lead to the securing of better results in the future than are now obtained. At the same time I think great caution is necessary in accepting the results of agglutinin and opsonin estimations as being true indices of the degree of immunity attained, and that these should on no account be allowed to usurp the place rightly belonging to clinical observations.

Lister found that the African natives displayed an extraordinary susceptibility to the pneumococcus and required very high dosages to ensure immunity. Although one particular type was found to be especially

prevalent and deadly, he employs a four-strain vaccine, containing 6,000 millions per c.c. of each strain, so that the total content is 24,000 millions per c.c. His initial dose of 1 c.c. of this is twice repeated at intervals of seven days. No interference with their work results therefrom, and their liability to infection is stated to have been materially reduced.

Borel found precisely the same to hold good for the Senegalese troops in France, and immunized them with initial doses of 28,000–32,000 millions without ill-effects.

The work of the Rockefeller Institute has shown that for white people initial dosages containing 1,000 millions of each of the prevalent strains can be safely employed, and that with lower dosages full immunity may not be secured. While confirming Lister's observations that very large dosages excite only slight reactions, they conclude from experiments upon animals that more effective and rapid immunity is secured by the frequent injection of smaller amounts than by the infrequent injection of very large amounts. Accordingly the initial dosage of 1,000 millions of each strain is adopted, after seven days either 1,000 or 2,000 million is given, and in either case a further 2,000 millions of each strain seven to ten days later.

My own experience has been that clinically very satisfactory results indeed are to be expected in England from the smaller scheme of dosages already given on pp. 95, 96; but these good results doubtless are partly to be attributed to my use of a mixed vaccine of the catarrhal organisms commonly associated with the pneumococcus, and no valid reason appears to exist for the use of initial doses containing less than 500 millions of each type commonly found in the country, provided one adequately assures oneself that the patient is not a carrier of the

pneumococcus in a lower lobe of the lungs. Should this be the case, very serious consequences indeed may result from the use of initial doses containing more than 50 millions of the particular strain with which the individual is infected. Whether with 50 millions of his own strain higher dosages, such as 250 millions, of each of the other prevalent strains can be safely combined I am unable to say, for I have never felt myself justified in adding more than a total of 50 millions of other types.

For healthy subjects, free from pneumococcal infection of the lungs, the initial dose in England for prophylactic purposes may be safely fixed at 250–500 millions of each prevalent strain; if, as expected, no general reaction result, this dose may be doubled after seven days, and this again doubled after a further seven to ten days; further and larger doses may be given subsequently if opportunity offer. For people with foci in the lungs the initial prophylactic dose should not exceed 50 millions of each type, and especially of the type corresponding to his infection, if this can be determined. The subsequent procedure will depend entirely upon the nature of the response to this initial dose.

Results.—The best published record of the results obtained upon any large body of men is that by Cecil and Austin (*Journal of Experimental Medicine*, July 1st, 1918, Vol. XXVIII. No. 1, pp. 19–41).

At Camp Upton, near New York, they inoculated 12,519 men against Types I, II, III, of Cole. Three or four doses were given at intervals of five to seven days, the total dosage being 6,000–9,000 millions of Types I and II, and 4,500–6,000 millions of Type III. During the ten weeks subsequent to the inoculations during which the men were under observation, no case of pneumonia due to these three types occurred among

men who had received two or more doses of vaccine; while in a control of approximately 20,000 men, there were twenty-six cases of pneumonia due to these types during the same period. It may be added that the incidence rate of Type IV pneumonia was also much less among the vaccinated than among the unvaccinated; while no explanation is given for this, it appears possible that a vaccine of one type affords some immunity against infection by a different type.

Small sterile infiltrations disappearing spontaneously occasionally followed the injection of large doses, and the same individuals were also prone to exhibit local reactions to each dose. These, however, caused no trouble and appear to be of no particular significance.

In a discussion of the prophylaxis of pneumonia it is necessary to bear in mind that the pneumococcus is not the only microbe capable of setting up this disease. It is, however, by far the most frequent cause of epidemics or pandemics of the lobar form. During the great epidemics of 1918 in practically every country affected it was determined that in the earlier part of the year there was an epidemic of the lobar form due to the pneumococcus, in which the case mortality was relatively low; this subsided, and was speedily followed by a much more virulent and general epidemic of the lobular or broncho-pneumonic type, in which the case mortality rose to 40 per cent. and even 60 per cent. in some localities. Although the pneumococcus was isolated both "in vivo" and post-mortem from the secretions, blood, and pulmonary tissues in a certain percentage of the cases, and the *B. influenzæ* and *M. catarrhalis* in a further larger percentage, the predominant microbe found in practically all these cases was a form of the *Streptococcus longus* characterized by strong haemolytic

powers, and therefore called *Streptococcus hæmolyticus*. No serious attempt was made upon any large bodies of men to raise their immunity to this microbe only; personally I included full doses of it in all my Combined Vaccine for Colds during 1917 and 1918, and, as I have mentioned on p. 98, not a single patient who had been through a full course of prophylactic inoculations during the preceding twelve months contracted the disease; this would certainly seem to indicate (1) that immunity against this microbe can readily be established if adequate dosages be employed; (2) that immunity against this microbe may be established at the same time as it is being raised against the *B. influenzae*, *pneumococcus*, *M. catarrhalis*, and such other catarrhal organisms as may be desired. Although the streptococcus group includes at least as many variants as the pneumococcus group, it is not necessary to include every known strain for this purpose, as some are definitely "local" or peculiar to certain localities. In catarrhal disorders, in addition to the *Streptococcus hæmolyticus* I have found to be concerned non-hæmolysing strains of the "longus," the "brevis" of the mouth, and the form described as "maximus" in my *Bacterial Diseases of Respiration*, p. 29, accordingly several strains of each of these types should be included in the vaccine for immunizing purposes.

What has been said regarding dosage with respect to the pneumococcus may be considered to hold good here; accordingly the doctor may either follow the procedure adopted by Lister and Borel and give a dose of 4,000 millions of each selected strain repeated at intervals of seven to twenty-one days, as has been found to be necessary and to give good results in the case of the susceptible black races, or follow the pro-

cedure which I have found to give quite satisfactory clinical results over many years in the case of my white patients as given on pp. 94, 95, a procedure receiving ample support from Cole's observations at the Rockefeller Institute.

Again I will point out that these dosages are only applicable to those who are altogether free from infection by this organism, but would mention that so far I have never met with a case of focal infection by the *Streptococcus haemolyticus*; doubtless many such cases will, however, be found in the future among those who have made delayed or imperfect recovery from an attack during the recent epidemic. In the case of these, as pointed out on p. 94, it will be necessary to adopt a course of "therapeutic" rather than of "prophylactic" immunization.

Anti-whooping-cough Inoculation.—The bacteriology of whooping cough affords another very good example of the rarity of pure infections. I have myself investigated a good many cases, and in only one instance found anything approaching a pure infection, and that was a chronic case in a boy of fifteen. The *B. influenzae* and *pneumococcus* may be said to complicate the infection in every instance. Hence the futility of employing a pure vaccine of Bordet's bacillus for therapeutic purposes is perfectly clear, and the inadvisability of using it for prophylactic purposes when it is just as easy to use one combined with *B. influenzae* and *pneumococcus* is equally obvious.

As regards dosages, the absurd idea held by some with regard to influenza vaccine crops up again in the minds of many, and unfortunately is handed on to the vaccine of *B. Bordet*, possibly because the two organisms resemble each other morphologically and

culturally and occur together. For years a large orphanage has been using my Combined Vaccine for Whooping Cough in the doses I advise without the slightest ill-effect even in the youngest children, and with the result that the annual visitations are no longer known. I am glad to say that the responsible authorities at St. Mary's Hospital have at last woke up to the non-toxicity of the vaccine and the necessity in prophylaxis of employing much larger dosages than formerly they recommended. The minimal amounts of the several constituents likely to be productive of real prophylactic benefit are as follows:

First dose:

Age.		B. Bordet.	B. influenzae.	Pneumococcus.
1-3 years	.	.	50	25
3-7 years	.	.	100	50
7-14 years	.	.	250	100
Over 14 years	.	.	500	250

Second dose:

Age.		B. Bordet.	B. influenzae.	Pneumococcus.
1-3 years	.	.	100	50
3-7 years	.	.	250	100
7-14 years	.	.	500	250
Over 14 years	.	.	1,000	500

Third dose:

Age.		B. Bordet.	B. influenzae.	Pneumococcus.
1-3 years	.	.	250	100
3-7 years	.	.	500	250
7-14 years	.	.	1,000	500
Over 14 years	.	.	2,000	1,000

Only in the very unlikely event of the patient reacting at all strongly to the second dose should the third one be maintained at the level of the second.

Dr. E. L. Shaw, in the *American Journal of Obstetrics*,

1917, fully confirms my views and results. After pointing out that at least 80 per cent. of the deaths in New York State during 1910-14 resulting from whooping cough were in children under two years and 96 per cent. in children under five years of age, he strongly emphasizes the urgent need of controlling and preventing a disease which takes such a heavy toll of young life and leaves such serious marks upon the survivors. He records the results by Graham and Hess at St. Margaret's House for Children, where prophylactic inoculation was introduced, as follows:

Prior to the introduction of this measure, fully 50 per cent. of the inmates contracted the disease at each epidemic; after its introduction 164 children were exposed to four different epidemics, and only 7 per cent. of them contracted the disease—this despite the fact that pure cultures of Bordet's bacillus were employed. The dosage given was 500 millions for the first, 1,000 millions for the second, and 2,000 millions for the third, at intervals of two to three days. Despite the short interval and the heavy dosages, heavier even than those I have given, they have found the vaccine quite harmless, productive of no severe reactions, and free from risk of anaphylaxis. Their conclusion was that “the value of vaccines as a prophylactic measure is undeniable, and they should be administered to every child exposed to whooping cough.”

Saunders and others (*Pediatrics*, March, 1912), while recognizing as the result of experience that their dosage was too small (viz. 10 to 20 millions), concluded that not only did the vaccine have a decided value as a prophylactic, but that it alone will absolutely prevent it. My experience of the very few cases that have contracted the disease after immunization with the smaller and

inadequate dosages I formerly advised was that in each case the attack was of very much milder character and shorter duration.

Bordet's bacillus is a difficult one to isolate, and requires very special media to secure anything like a free growth, so adequate dosages of a reliable vaccine are costly to produce and can never be sold at a low price; none the less it affords such a relatively cheap insurance against such a fatal and pernicious complaint that the wise doctor will in future never fail to advise prophylactic inoculation of the other members, and especially of the young members, of a household of which one member has contracted an attack.

Antirabic Inoculation.—This is a procedure best carried out at one of the Pasteur Institutes established for the purpose, and the general practitioner in this country is little likely to be called upon to perform it. Inasmuch, however, as the material used, *i.e.* the dried cords of artificially infected rabbits, undoubtedly contains the undiscovered virus of the disease, the procedure is one of vaccine prophylaxis and requires mention for the sake of completeness. Its rarity, however, does not justify the full description of such a complicated technique in a small book of this description, and the reader is referred to such works as Kolmer's *Infection, Immunity, and Specific Therapy*, p. 685.

Anti-anthrax Inoculation.—This again is only mentioned for the sake of completeness and for its historical interest, inasmuch as the immunization of sheep against anthrax was made a test case for the establishment of Pasteur's reputation. Its usefulness in this direction may be well gauged from the fact that in France alone over $3\frac{1}{4}$ million sheep received inoculations within twelve

years, with a mortality rate under 1 per cent. against a preceding one of 10 per cent. A vaccine free from spores may be prepared either according to Pasteur's technique by growing the bacilli at a temperature of 42° C., or by subsequently thoroughly washing cultures grown at 37° C. As the disease in man, in view of its rarity, must manifest itself before infection can even be suspected—there is little or no call for prophylactic treatment in human beings.

Anti-scarlet-fever prophylaxis rests on no sound bacteriological basis, despite the vast amount of work done in Russia by Gabritschewsky and others. The true infective agent remains undiscovered, being probably a filterable virus, the *Streptococcus conglomeratus* found in the throats of all scarlet-fever patients being almost certainly nothing but a secondary infection. Gabritschewsky and others, however, up to April of 1908 gave over 37,000 prophylactic inoculations with a vaccine of this organism, and recorded extraordinary success—for instance, 4,771 people were inoculated in certain villages where the incidence rate among the uninoculated varied from 15 to 70 per cent. Of these, 2,034 received two or three injections, only two of these were attacked; the remaining 2,737 had only one inoculation, of these forty-one were attacked but most only very mildly. In the years subsequent to this date the work has been carried on in many villages in Russia with continued good results.

A paper by R. M. Smith (*Boston Med. and Surg. Journal*, February 21st, 1910) gives a complete résumé of the work.

Prophylaxis against *B. Coli* and other Intestinal Organisms.—Wright advocated the administration of a prophylactic dose of *B. coli* vaccine prior to abdominal

operations in which danger of sepsis and resultant peritonitis was to be apprehended.

A few abdominal surgeons have adopted his suggestion, giving either 500 or 1,000 millions a few days prior to the operation. Statistics and proof of the value of the proceeding are lacking, but inasmuch as these surgeons have used these doses of the vaccine for many years, their clinical impression obviously is that the prophylactic administration of the vaccine does diminish the danger of a peritoneal infection, should a few *B. coli* escape into the abdominal cavity.

A combined vaccine of particular value in this connection has recently been advocated. It contains 500 millions each of *B. coli* and streptococcus and 2,000 millions staphylococcus, all of abdominal origin. As in addition a certain percentage of sensitized organisms is added, the resultant immunity speedily attains reasonable dimensions; at the same time if it can be given not less than seven days nor more than twenty-one days prior to the operation, so much the better.

Immunization against Hay Fever.—Although it is exceedingly doubtful if bacteria are concerned at all in the causation of hay fever, except in so far as possibly their toxins add to the excitability and irritability of the mucous membranes of the part concerned, yet the process is so analogous to that of antibacterial immunization both in theory and method that space may be allowed it here. The toxins of twenty-five different grasses and seven kinds of flowers, varying in each country and locality, acting upon the excitable mucous membrane of the eye and nose, have been shown to be capable of giving rise to an attack; and the procedure in prophylaxis consists in (1) determining the variety of toxin to which the individual is susceptible;

(2) preparing the solution of toxin for use as an immunizing agent; (3) estimating the excitability of the mucous membranes; (4) and from this the appropriate initial dosage of toxin, and immunizing in the usual way.

Steps (1) and (2) as above are usually done in the experimental laboratory, (3) and (4) being left to the doctor.

It has been determined for this country that the pollens of "*Phleum pratense*" and of rye grass contain the toxin which most commonly gives rise to hay fever; the pollen of certain other grasses is also responsible, but to a minor degree, and the antitoxin to the toxin of the former also appears to be a suitable antibody to the latter. In America various other grasses and flowers have been found responsible.

A gram of each of the pollens of *Phleum pratense* and rye grass is thoroughly extracted with 50 c.c. of water by freezing and other methods, and for convenience sake each c.c. of the resulting solution is held to contain 20,000 units of toxin. Dilutions of this are made containing 5,000, 1,500, 500, 150, 50, 15, and 5 units per c.c.

Two or three drops of each dilution are put up in capillary glass tubes, and are used for a test upon the ocular conjunctiva in precisely the same way as a Calmette's test is made, a beginning being made upon one eye with the weakest dilution. If no reaction appears in two to three minutes, the next highest dilution is tried upon the other eye, and so on, until a reaction is obtained with a certain strength. In this way the susceptibility is demonstrated. This procedure has necessarily to be conducted well in advance of the hay-fever season. Formerly the initial dosage for im-

munization purposes was held to be one-third of a c.c. of the strength which gave the reaction. Clinical experience has, however, shown that higher initial dosages may safely be employed for immunization purposes, especially if treatment be begun at least one month before the first onset of the hay-fever season, the above dosage being reserved as the initial dose for treatment of an actual attack. Fifty to a hundred units may safely be given as the first dose. If 50 are given, 100 should be given five days later. If 100, 250 may be the second dose. To secure good immunity, a total of at least 1,000 units and preferably of 2,000 units should be given. If a slight attack be initiated by any given dosage, that dose should be repeated once or twice at five-day intervals before proceeding to the next dosage. While the percentage of cases in whom complete immunity is secured probably does not exceed forty, in about another 40 per cent. the attacks are rendered very much less severe.

CHAPTER VI

VACCINE TREATMENT OF "CARRIERS"

A "CARRIER" being a person that harbours somewhere in or on his tissues certain microbes which fail at the time to exert any detectable pathogenic action upon these tissues, it follows that the vaccine treatment of a carrier is much more closely related to prophylactic than to therapeutic treatment. Careful serological tests indicate that the tissues of true carriers entirely fail to respond to the presence of these microbes by the elaboration of any of the corresponding antibodies; the tissues therefore are not "sensitized" by the bacterial proteids, and any scheme for proposed inoculation should be based upon that found suitable for prophylaxis. This obvious truth has not received due recognition, with the result that much of the vaccine work done upon carriers is vitiated by the inadequate dosages employed. I speak above of **true** carriers, because the term carrier is sometimes used in what I consider a careless and slipshod manner. For instance, a person is spoken of as being a typhoid carrier who is presenting no symptom of typhoid fever, but, harbouring the bacilli in his gall-bladder, presents mild symptoms of cholecystitis, and is found to have a raised opsonic index and agglutinins in the serum. One might just as well speak of a person with periostitis due to *B. typhosus* as a carrier.

The chief infections in which carriers are most prone

to be found, and where the existence of these has been proved to be of very great importance in the initiation of epidemics, an importance so great that the extinction of the carrier may almost be held to be synonymous with the extinction of epidemics, are: (1) meningococcus; (2) diphtheria B.; (3) dysentery B.; (4) typhoid B.; (5) *V. cholerae*; (6) pneumococcus; (7) *B. influenzae*; (8) *Streptococcus haemolyticus*.

Keen and bitter discussion has ranged around the carrier question, especially in respect to his importance in cerebro-spinal meningitis. The fact already mentioned that carriers of a germ appear to fail entirely to elaborate any antibodies to that germ is, in my opinion, no evidence for or against the possession of virulence by the microbes, but is simply indicative of the fact that for the time being they are resident not strictly within the tissues but simply on their surface; they are maintaining a purely saprophytic existence. If this be so, the difficulty of successfully treating a carrier by means of a vaccine becomes of easy understanding, for if the germ be **outside** the tissues, it matters little how great may be the amount of antibodies which we may induce to circulate **through** the tissues. None the less, so great is the importance of carriers to the community, that I feel that their treatment by means of vaccine should receive a much more extensive study, carried out with a much better appreciation of the importance of the dosage question. In such an investigation it will also be necessary to determine whether the use of an autogenous vaccine or of a stock one of proved immunizing powers is to be preferred. I am inclined to think that the autogenous vaccine may be found defective, and that the stock one, compounded of strains as far as possible identical with that of the carrier, will be found the more efficient.

(I) **Treatment of Meningococcus Carriers.**—Every one conversant with meningococcal work will fully appreciate the difficulty of appraising with any accuracy the value of vaccine treatment of meningococcal carriers, the cocci having such a tendency to appear and disappear. For test purposes it will be necessary first to select cases from whom the meningococcus of a given type can be isolated with constancy, then to segregate each individual, so that all risk of reinfection or of infection by another type from another carrier may be obviated. Insufficient attention has been paid in the past to these two important points. This is the case with the small amount of work done on the question by Colebrook and Tanner (*Journal R.A.M.C.*, January 1916, p. 76, to which I refer reader for details), who also failed to consider the question raised above touching the composition of the vaccine.

They treated ten carriers with a vaccine killed by heating to 55° C. for half an hour and prepared from seven strains, six of these being from carriers, the seventh derived from cerebro-spinal fluid. A rising scale of doses was employed, culminating in one which gave a slight general reaction, corresponding approximately with the doses which Sophian had found to determine in the blood a maximal power of fixing complement. These doses ranged from 50 to 2,000 millions, and were given, some subcutaneously, some intravenously. The effect is very difficult to determine, and is further complicated by the fact that six of the cases lived together under conditions which admitted readily of reinvasion by the microbe after a carrier once became free of it—a state of affairs which, as I have already pointed out, should be rigidly excluded.

Of the ten carriers, five gave negative swabs after 5,

7, 13, 21, 27 days; the other five retained their meningo-cocci for some weeks in undiminished numbers. They concluded that no very striking advantage was gained from the inoculations. However, I would point out that "a rising scale of doses was employed, **culminating** in one which gave a slight general reaction." As I have so often said, no benefit can be readily anticipated from any dosage which fails to produce a slight general reaction, so that their **final** dose was **approximately** of the dimensions appropriate to a correct initial dosage. In view of the fact that they could detect no beneficial effect from any other method of treatment, I would suggest that if any of my readers have such a carrier to treat, they begin vaccine treatment either with an autogenous vaccine or with a polyvalent stock vaccine compounded of virulent members of the same type as that infecting the carrier, and that they begin with such a dosage as they would employ for prophylactic purposes, *i.e.* certainly not less than 500 millions and preferably with 1,000 millions.

(2) **Diphtheria Carriers.**—Of the treatment of carriers of the Diphtheria bacillus with vaccines little is to be found in the literature.

Walton Smith (*Australian Med. Gazette*, October 20th, 1910, p. 543) tells of a girl in whose throat the bacilli were found, along with staphylococci, fifteen weeks after antitoxin was given, recovery being apparently complete. A first inoculation with 6 million *B. diphtheriae* and 10 million *staphylococcus* resulted in the production within twenty-four hours of a well-marked local reaction and some general reaction, the temperature rising to 100.3° F. Seven days later, the bacilli being still present, a second dose of 8 million *B. diphtheriae* was given. A very slight reaction ensued, and thereafter the Klebs-Loeffler bacillus could not be found.

(3) **Dysentery Carriers.**—With the return of the army from abroad the successful treatment of the carrier of the dysentery bacilli is going to assume a very great importance, and the general practitioner will have to face the problem no less than the specialist and army doctor, for many cases are certain to escape detection prior to demobilization, and what steps Army or Government will take once they have been discharged Heaven only knows ; possibly they will be left to the proposed State Service to deal with. Long before arrangements are officially made, the doctor will be face to face with the problem, and upon him will depend whether bacillary dysentery is to become endemic or not in the United Kingdom. In Chapter V we have seen how the difficulties of preparing a satisfactory vaccine have been overcome, and I am convinced that much will turn upon the question of the value of this vaccine in the treatment of carriers. So far as I know, nothing has yet been done in this direction, but I think a word of warning is here necessary. It will always be a matter of doubt as to how far any given individual is a true carrier. Only a very small percentage probably will be ; in the great majority it will simply be a matter of persistent infection by organisms of diminished or very low virulence. The case of dysentery which has made a complete recovery and is free from symptoms of every kind is a rarity. Most exhibit mild symptoms of a kind, and it will be next to impossible in the case of a carrier to decide whether or not these are due to the persistence of infection. This is all-important from the point of view of dosage, and until a considerable amount of experimental work has been done by responsible individuals, great caution should be exercised with regard to dosage, and I certainly advise the enterprising doctor

not to assume that these cases are true carriers and treat them with prophylactic doses, but for the time being rather to regard them as infected individuals and dose them accordingly. As he gains experience, so may he become more daring. An initial dosage of 100 millions, best of a sensitized autogenous vaccine, may, I think, be safely risked, and be repeated at an interval of seven to ten days, before raising it to 250 millions, and hope of cure should not be given up until (a) an ultimate dosage of 1,000 millions has been given a good trial, unless severe reactions contra-indicate it ; (b) in the event of the autogenous vaccine failing, a course of treatment with a stock vaccine of proved immunizing power and conforming exactly in type to the infective organism has also been tried.

(4) **Typhoid Carriers.**—Adhering to the strict definition of a carrier as being one who presents no symptoms whatever of the bacterial infection, and accordingly reserving the consideration of cases presenting symptoms, however mild, of cystitis, cholecystitis, etc., till Chapter XII, wherein I deal with therapeutic immunization, it becomes necessary to exclude here certain cases described as “carriers,” but presenting definite signs of bacterial infection, which have been cured by means of vaccine. There remain a few cases of true carriers that have been successfully treated. Inasmuch as no other treatment appears to be of the slightest avail, I here describe two such cases in detail. The first was reported by Irwin and Houston (*Lancet*, January 30th, 1909, p. 311). The patient had been excreting for seven years large numbers of bacilli in the urine but none in the faeces. A dose of 50 millions produced malaise, headache, and some rise of temperature, 100 millions eight days later producing a milder reaction;

200 millions were given after eighteen days. Two days later the urine was crowded with bacilli, but eighteen days later they had completely disappeared. Further doses of 300, 500, and 1,000 millions were given at fortnightly intervals. The patient improved considerably in general health and gained ten pounds in weight. Observation was kept on the urine for two years, but the bacilli were never again discovered. Houston has since recorded three similar cases, two being completely cured, the third greatly improved.

Currie and McKeon (*Jour. Amer. Med. Assoc.*, January 18th, 1913, p. 183) give details of a carrier who had infected twenty-eight other people, four of these dying. The attack of typhoid fever dated back five years, and recovery was apparently complete, but six months later *B. typhosus* was isolated from the faeces, and during the subsequent three months on eleven occasions ; the urine, on the other hand, was always sterile. He received ten doses of vaccine in two months in the following dosages : 25, 50, 125, 250, 500, 250, 400, 400, 1,000, 1,500 millions, the first general reaction being noticed with the 500-million dose, as would be expected in the case of a true carrier. The search for the bacillus was continued for three and a half months after the conclusion of treatment, but it was never found again.

Equally successful results have been reported by others, so that in vaccine we appear to have a reliable agent for bringing about cure in these cases, fraught as they are with so much danger to others with whom they may possibly come in contact.

Dosage.—The danger of over-dosage of a true typhoid carrier being certainly less than in the case of the dysentery carrier, as the diagnosis of the patient being really a carrier and a carrier only is made with greater ease

and certainty in the case of the former than in the case of the latter, a somewhat higher initial dosage may be adopted. Those who have recorded cases have as a rule been careful to note the numerical dosage at which the first signs of a reaction appeared. In only one case has this been with a dosage of less than 250 millions, so I think this figure may safely be adopted as our initial dosage. An autogenous vaccine, whilst obviously certain to conform to "type," may possibly possess little power of inciting antibody formation, as owing to the long residence of the bacillus in or on the tissues it may have accustomed itself to the antibodies in the tissues, if any such have been formed, and, as it were, have immunized itself against these antibodies, a power which we well know pathogenic organisms to possess. If, therefore, the autogenous vaccine—and in every case where possible I think an autogenous vaccine should receive first trial—fail to cause any reaction or apparent improvement of the condition, a stock vaccine of proved immunizing power should then be employed, but in this case thorough investigation into the type of the infective organism must be made and the corresponding vaccine obtained, for obviously it will be little use employing a vaccine of *B. typhosus* if the patient be "carrying" *B. paratyphosus A* or *B.*, or a vaccine of *B. paratyphosus A* if he be carrying *B. paratyphosus B*. Intervals of seven to ten days may be appropriate, and each dosage should be repeated at least once before being doubled. An ultimate dosage of 1,000 millions, or even 2,000 millions, should be attained before hope of success is abandoned.

(5) **Cholera Carriers.**—A few cases of "carriers" of the *V. cholerae* or its near associates are on record, but I can find no mention in the literature of such a

case receiving vaccine treatment. As an aftermath of the war, I think that cholera carriers may possibly come more into evidence, if not among our returned prisoners of war, certainly in those armies among whom cholera epidemics raged on more than one occasion. If this prove to be an intelligent anticipation, it is to be hoped that the possibilities of successful vaccine treatment will be borne in mind. An initial dosage of 100 millions of a well washed agar culture may be suggested.

(6) **Pneumococcus Carriers.**—In view of the well-known fact that a very large percentage of healthy individuals harbour in the mouth an organism which, until very recently, was indistinguishable from the pneumococcus causing pneumonia, the presumption has been frequently made that most pneumonic infections are to be considered as auto-infections, and that the important factor in determining the incidence of the disease is variation in susceptibility brought about by exposure, chill, or other accidental occurrence. The very careful and systematic study of the disease conducted over several years at the Rockefeller Institute already referred to has conclusively shown the fallacy of this. Avery, Chickering, Cole, and Dochez made a comparative study of the relative frequency with which their "Type" pneumococci were to be isolated from the mouths of healthy persons who had not come into recent contact with a case of pneumonia and from the mouths of pneumonia patients, comparing the results from 297 cases of the former and 454 cases of lobar pneumonia. The subject is of sufficient importance to justify the inclusion of the following comparative tables. In the mouths of the 297 healthy cases the pneumococcus was found 116 times, in a few instances those of more than one type being present.

TABLE A

DISTRIBUTION OF DIFFERENT TYPES OF PNEUMOCOCCUS
IN THE MOUTHS OF NORMAL PERSONS

Type of Pneumococcus.	Times found.	Percentage Incidence.
I	1	0.8
II	0	0
II _a	1	0.8
II _b	7	5.8
II _x	14	11.6
III	34	28.1
IV	64	52.9

TABLE B

TYPES ISOLATED FROM CASES OF PNEUMONIA

Type.	Times found.	Percentage Incidence.
I	151	33.3
II	133	29.3
II _a	6	1.3
II _b	4	0.9
II _x	9	2.0
III	59	13.0
IV	92	20.3

Comparison of these two tables shows that the pneumococcus most commonly found in the mouth secretions of healthy individuals gives rise to a minority of cases of lobar pneumonia, and that Types I and II, which cause a majority of cases of lobar pneumonia, are of high virulence for human beings, and are seldom or never found in the mouths of normal individuals who have not been in intimate contact with cases of lobar pneumonia, thus indicating that pneumonia originates as an infection from without. With their results and general conclusions I am in entire accord, but with their final conclusion I entirely differ. In my opinion, pneumonia in white races almost invariably

originates from within, but pneumonia seldom attacks any individual except those already possessing foci of pneumococcal infection in their lower lobes; foci which are seldom indeed detected by the average doctor, and are consequently ignored by almost every bacteriologist. As I have said, these foci may exist for very many years, without causing any marked symptoms in the patient, except when the bacteria spring into activity and increased virulence, giving risk to nasal, tracheal, and bronchial catarrhs, and if neglected to pneumonia. At these times the pneumococci are of course to be found in the mouth, at other times they may or may not be present.

By the kindness of the Rockefeller Institute I was given a supply of the various test antisera, and determinations of the Type Pneumococcus isolated from eighty of these carriers give results almost identical with those not in Table A, but in Table B, in itself very strong proof of the accuracy of my views.

These cases, now that I am thoroughly familiar with them, almost invariably present recognizable signs and symptoms, and therefore are not truly "carriers." In the eyes of those unacquainted with the symptomatology they would rightly be styled "true carriers," and at times certainly the symptoms are so slight as almost to justify the application of the term.

To the presence of these carriers in our midst we are indebted, and of this I am absolutely certain, for the initiation of all epidemics of pneumococcal colds, of influenza, and of pneumonia, and could the foci existent in the lower lobes of each and all of them be eradicated, catarrhal epidemics due to this organism would wholly disappear from our midst, except in so far as they were introduced by immigrants from without. Unfortun-

ately this task is one of the most difficult in the whole of vaccine therapy. What, however, is easy, and this almost amounts to the same thing, is by means of proper vaccine treatment to keep the virulence of the microbes resident in the tissues at such a low virulence that they find extreme difficulty in extending the area of their operations and giving rise to an acute infection in their unwitting and unwilling host. The treatment proper to these cases therefore must be twofold: first, their therapeutic immunization with the object of eradicating the focus, or, if this prove impossible, of ameliorating the condition in so far as this proves possible; secondly, their prophylactic immunization to prevent recurrence in those who have been cured or to maintain the virulence of the infecting microbes at the lowest possible level in those whom we have failed to cure. The former object is dealt with subsequently in Chapter VIII; the latter has already been fully discussed in Chapter V. It therefore only remains for me here again to insist on the prime importance of determining the exact type, according to Rufus Cole and Lister, of the infecting microbe, both from the point of view of therapeutic and prophylactic immunization, and the necessity of employing adequate dosages, especially in the case of the latter objective. A series of three subcutaneous doses of 1,000, 2,000, 4,000 millions of the autogenous or type-true stock vaccine, combined with half these dosages of each of the other strains, given at seven-days' intervals twice yearly, is not excessive, and is little likely to give rise to any undesirable reaction, except in rare hypersensitive cases—and whether the case is one of these will be learnt during the course of therapeutic immunization. Should the intravenous route be selected—and certain experiments

seem to prove that this method brings about a more speedy and complete formation of antibodies—it will be advisable to reduce the dosages I have recommended by about three-quarters.

(7) **Influenza Carriers.**—What I have said about pneumococcus carriers applies equally to carriers of the *B. influenzae*, the more especially as the two bacteria are frequently associated at the foci of infection which I have described in the lower lobes. I have known of many cases, apparently pure infection by the pneumococcus, but I cannot recall a single case of pure focal infection by the *B. influenzae*, the accompanying microbe being usually the pneumococcus, sometimes the streptococcus, rarely the *M. catarrhalis*.

Inasmuch as the advent of a virulent infection by the *B. influenzae* has a most potent influence upon the virulence of the pneumococci in these foci, the advisability is obvious of combining prophylactic immunization against the *B. influenzae* with the prophylactic immunization against the pneumococcus; this can be easily done by adding a dosage of at least an equal number of stock polyvalent *B. influenzae* vaccine to the prophylactic doses of the pneumococcus.

(8) **Carriers of Streptococcus haemolyticus** have assumed a vastly increased importance from the researches of numerous workers in America, France, and this country upon the rôle they have played in the dissemination of the pandemic of acute pulmonary disease during 1918-19. Cole has shown conclusively the ease with which this microbe is transmitted from one individual to another; and Levy (*War Medicine*, November 1918, vol. ii. No. 4, p. 560) mentions how in a ward reserved for "clean" cases (*i.e.* those in whom no streptococci were to be found in throat swabs and cultures), throat cultures

made at intervals of a few days revealed the fact that several "clean" cases were being converted into carriers. On swabbing the personnel of the ward, it was found that two orderlies and one nurse harboured *Streptococcus haemolyticus* in profusion in their throats. On replacing these individuals with non-carriers, no further contamination occurred. Attempts at mouth and throat disinfection have proved singularly unsuccessful. Thus Dakin's solution in half strength as gargle and spray is useless, as it will not kill this organism even "*in vitro*." Iodine in glycerine, while successful in the test-tube, is clinically most disappointing, and the same is true of dichloramine and zinc sulphate. The organisms safely harboured in tonsillar crypts and the lymphatic tissues of the nasopharynx are not accessible to local treatment. As vaccine treatment has not yet been given an adequate trial, it is impossible to say whether it will succeed where other remedies fail, and the best available procedure at present is to make all infected cases wear a mask over the nose and mouth of four or five folds of good butter-muslin (**at least** ten threads to the inch), and to cause all "clean" cases to do the same when they are about to come into contact with infected cases. These masks should be sterilized daily by soaking for one hour in a 2 per cent. solution of lysol, cresol, or other convenient antiseptic, and then boiling for thirty minutes in soap and water.

CHAPTER VII

THERAPEUTIC IMMUNIZATION : INTRODUCTORY

IN Chapter V we have considered procedures carried out almost entirely by rule of thumb, where little or no attention is directed to reactions, local or constitutional, except in so far as they indicate a likelihood of difficulty being encountered in attaining the desired high ultimate dosages. In Chapter VI we have dealt with another class of case, where again reactions are of no great import, except in so far as they may be indicative of the case not being a true carrier, but one wherein there is a latent or not very obvious focus of infection, necessitating change in our point of view and transfer of the case to the class of therapeutic immunization.

Now we have to deal with the conduct of cases where reactions become of paramount importance, insomuch as they furnish us with our most dependable guidance to dosage and intervals. Now, success in treatment will vary almost directly with the care and skill we devote to our observation of these.

The **local** reaction is, as we have seen, of little import.

The **general** reaction is a measure of the toxins circulating in the tissues and derived in small part from the dose of bacilli given, in major part from the bacilli killed off and lysinized at the foci of infection ; it is also probably some guide to the amount of antibody formation, and is a warning that the tissues are making

a response, approaching a maximal, to the stimulus supplied by the vaccine. It is therefore necessary to avoid giving rise to any general reaction excessive in kind or degree, for, as we have seen, ample evidence exists that stimuli of a certain magnitude excite the formation of maximal amounts of antibodies, and stimuli in excess of these not only do not give rise to any further formation of antibodies, but even cause the disappearance of a certain proportion of those already present. The same observations show that the most desirable stimulus corresponds to a general reaction of moderate degree, such as I have described on p. 54. If this stimulus be properly adjusted, the formation of antibodies follows so rapidly on the liberation of the toxins that these latter are almost immediately neutralized, and the period of lowered resistance or **negative phase**, as it is called, becomes strictly limited to a few hours, or to so short a duration as to escape all but the most careful scrutiny. The period of toxin formation and lowered content in antibodies is indicated by rise of temperature, accelerated pulse, and headache and feeling of slight malaise; the period of toxin neutralization and increased output of antibodies by fall in temperature, slowing of pulse, feeling of well-being and general clinical improvement.

In cases of generalized infections without obvious foci and in cases of localized infections where observation, direct or indirect, of the foci is not possible, dependence for control of dosage and intervals must be placed upon the **general** reaction.

In cases where the conditions obtaining at the focus of infection can be kept under close observation, our most important guide as to the sequence of events occurring there is constituted by the **focal** reaction.

The general nature of the focal reaction has already been described on p. 54. It of course depends on the site and nature of the lesion.

If this be a conjunctivitis or corneal ulcer, affection of the skin or subcutaneous tissues, or any superficial lesion, it can of course be at all times kept under direct observation. If, however, it be more deeply situated, as for instance a pneumococcal infection of the bronchi or a lobe of the lung, it cannot be kept under direct observation, but changes occurring there can be deduced with almost mathematical accuracy from careful stethoscopic observations, and by examinations, bacteriological and cytological, of the sputum. These observations must be properly spaced in time and conducted in a thorough and methodical fashion. In this connection I must point out things to which rarely sufficient attention is directed: (1) the absolute necessity of observing thoroughly the lower portions of the lung, back and front, and those in the axillary region; (2) the great importance of post-tussic auscultation. There is many a lung presenting no auscultatory signs whatever to the casual observer, yet presenting most definite signs when the patient is made to give a cough initiated by diaphragmatic contraction followed by a sharp deep inspiration.

No amount of verbal explanation will convey to the reader so precisely the cycle of changes which occur in infected pulmonary tissues in response to the administration of an appropriate dose of vaccine as will their diagrammatic representation. I therefore reproduce here a series of charts from my book *Bacterial Diseases of Respiration*, which show graphically the changes produced in the chest of a case of chronic bronchitis under treatment with a mixed vaccine. These will be discussed fully in the following chapter.

Front of Chest

	R.				L			
 = POST-TUSSIC RÂLE	○	○	○	•	I	○	○	•
	X.	X		○		X.	X.	○
 = PRÆ-TUSSIC DRY-RÂLE	•	X	○	X	II	•	•	•
	X	○	•X	○		X	○	X.
 = PRÆ-TUSSIC MOIST-RÂLE	○	•	○	○	III	X	○	○
	X	•	○	X		X	•	•
 = RHONCHUS	○	○			V			
	X	X						

Back of Chest

L.				R.		
• ○	×	° x	I	× ○	• ○	×
• ○	×	° ○ ○	II	• x ○	° x ○	×
× ° • •	×	x	III	× ○ •	° ○ •	○
• ○ •	×	° • ○	IV	○	× ○ •	○
• ° •	° •		V	• ○ •	° •	
• •	×	° ○	VI			
			VII			

CHART I.—Before first inoculation. Sputum = 6 oz. per day.

Front of Chest

	R.				L.		
	•	•	•		•	•	•
POST-TUSSIC RÂLE	X	○ X	○ X	I	X ○	X ○	X
	○	X ○	○		○ X	X ○	○
PRÆ-TUSSIC DRY-RÂLE	○ X	○ X	○ X	II	X	X ○	○
	X ○	X ○	X ○		○ ○	○ X	X ○
PRÆ-TUSSIC MOIST-RÂLE	○	○ ○	○ X	III	○ X	○ ○	○ X
	○ ○	○ ○	○ ○		○ X	○ X	○ ○
○ ○ ○ = PRÆ-TUSSIC MOIST-RÂLE	○	○ ○	○	IV	○ ○	X ○	○
	○	○ ○	○		X ○	X ○	X ○
RHONCHUS	XX	○ ○	○	V	○ ○	○ ○	○ ○
	X	○ ○	○		○ ○	○ ○	○ ○
	•	○ ○	○		•	○ ○	○ ○

Back of Chest

	L.				R.		
	•	•	•		•	•	•
X ○	X ○	X ○	I	X ○	X ○	○ ○	○ ○
X	○ X	X ○		○ ○	X ○	○ ○	○ ○
○	X ○	○ X	II	○ ○	○ ○	X ○	○ ○
X ○	X ○	X ○		○ ○	○ ○	○ ○	○ ○
○	X ○	○ X	III	X ○	○ ○	X ○	X ○
X ○	X ○	X ○		○ ○	○ ○	○ ○	○ ○
○	X ○	X ○	IV	X ○	○ ○	X ○	○ ○
X ○	X ○	X ○		○ ○	○ ○	○ ○	○ ○
○	X ○	X ○	V	○ X	○ ○	○ ○	○ ○
○ ○	X ○	X ○		○ ○	○ ○	○ ○	○ ○
○ ○	X ○	X ○	VI	○ ○	○ ○	○ ○	○ ○
○ ○	X ○	X ○		○ ○	○ ○	○ ○	○ ○
	○ ○	○ ○	VII	•	•	•	•
	○ ○	○ ○					

CHART II.—Twelve hours after first inoculation. Sputum = 10 oz. per day.

Front of Chest

	R.				L.		
○○○ = POST-TUSSIC RĀLE	○	○	○	I	○	○	○
○○○ = PRĀ-TUSSIC DRY-RĀLE	○	○	○	II	○	○	○
○○○ = PRĀ-TUSSIC MOIST. RĀLE	○	○	○	III	○	○	○
XX = RHONCHUS	○	○	○	IV	○	○	○
	○	○	○	V	○	○	○
	○	○	○		○	○	○
	○	○	○		○	○	○

Back of Chest

	L.				R.		
○○○	○	○	○	I	○	○	○
○○○	○	○	○	II	○	○	○
○○○	○	○	○	III	○	○	○
○○○	○	○	○	IV	○	○	○
○○○	○	○	○	V	○	○	○
○○○	○	○	○	VI	○	○	○
○○○	○	○	○	VII	○	○	○

CHART III.—Twenty-four hours after first inoculation. Sputum = 6 oz, per day.

Front of Chest

					R.			L.
• = POST-TUSSIC RÄLE	•	X	•	I	○	•		
• = PRÆ-TUSSIC DRY-RÄLE	•	○ X		II	X	•	•	•
○○ = PRÆ-TUSSIC MOIST-RÄLE	X	○ X	X	III	•	•		•
XX = RHONCHUS	•	○	•	IV				
				V				

Back of Chest

					L.			R.
•	○	○	I					
•	X	○	II	X	•	X		
•	○	○	III	•	•	X	•	
•	•	○	IV	X	•	•	•	
			V					
			VI					
			VII					

CHART IV.—Seventy-two hours after first inoculation. Sputum = 2 oz. per day.

Front of Chest

	R.					L.
$\bullet\bullet\bullet =$ POST-TUSSIC RÂLE	o X	o o X o		I		
$\bullet\bullet\bullet =$ PRÆ-TUSSIC DRY-RÂLE	o X o o	o X o o	o X o o	II	x. .	x. .
$\bullet\bullet\bullet =$ PRÆ-TUSSIC MOIST-RÂLE	o o o	o X o o	o X o o	III	• x	• •
$\times\!\times =$ RHONCHUS		o o o	o o o	IV		
				V		

Back of Chest

	L.					R.
	x			I		
	x. .	.		II	o X o	o x. .
	.	.		III	• o o	• o x
				IV	• o o	• x o
				V	• o o	• o •
				VI	• o o	• o •
				VII		

CHART V.—Six days after first inoculation. Second inoculation,
Sputum = 3 oz. per day.

Front of Chest

Back of Chest

L.				R.		
x o	x o	.	I	o x	o	
x o x	x o x	o	II	o x o	x o o	.
x .	x o x	o	III	o o	o o	.
	o .		IV	o o	x o	o
			V	o o	o o	o
			VI	o o	o o	o
			VII	o	o	o

CHART VI.—Twelve hours after second inoculation. Sputum
= 4 oz. per day

Front of Chest

				R.				L
					I			
$\text{X} \text{ } \text{O}$ = POST-TUSSIC RÂLE	X	X	O					
$\text{O} \text{ } \text{O}$ = PRA-TUSSIC DRY-RÂLE	X	O	O		II		.	O
$\text{O} \text{ } \text{O} \text{ } \text{O}$ = PRA-TUSSIC MOIST-RÂLE	.	O	O		III			
$\text{X} \text{ } \text{X}$ = RHONCHUS					IV			
					V			

Back of Chest

				L				R.
*	.							
*	.	*			II	.	*	*
					III	.	*	*
					IV	.	*	*
					V	.	*	
					VI	.	*	
					VII	.	*	

CHART VII.—Forty-eight hours after second inoculation.
Sputum = $\frac{1}{2}$ oz. per day.

In the combination, then, of judiciously provoked general and focal reactions we have an ample and accurate guide to the dosage and intervals appropriate to the conduct of a case undergoing therapeutic immunization. Should a general reaction be lacking, reliance must be placed on the focal reaction, combined with observations of the general clinical condition. Should the focal reaction be absent, then reliance must be placed on the general reactions combined with clinical observations. In the rare event of both focal and general reactions being absent or impossible of observation, then experience and clinical observation must be our guide. As a general rule it may be taken that the more acute the infection the more nearly it approaches to becoming generalized, and the more toxic the case the smaller is the initial dosage appropriate to the case. For instance, while an initial dose of 100 millions of a pneumococcal vaccine may safely be given to a case of chronic pneumococcal infection of the lung, an initial dose of 50 millions is to be preferred for an early case of acute pneumonia, and of 25 millions if the case appear to be a fulminating one with marked symptoms of toxæmia, whilst a further reduction to 10 millions may be made if the case be one of septicæmia. The effect of this initial dose must be closely watched, the focal and general reaction and changes in clinical condition observed, correlated, and interpreted, in order to estimate the immunizing response to the stimulus thus given. A slight rise in temperature of 0.5° F.- 1.5° F. and in pulse-rate of ten to twenty beats occurring in the first few hours, and followed within twelve to twenty-four hours by a fall in the same to below the previous level, a slight feeling of headache and malaise similarly passing off and being succeeded by a feeling of increased well-being

and better appetite, an improved action of the skin, bowels, and kidneys, are all signs of a mild and desirable **general** reaction.

Similarly, an increased hyperæmia around the lesions accompanied perhaps by slightly increased pain, swelling, and secretion, increase of cough and expectoration, increased physical signs in the lung with additional moist signs—all these, passing off within twelve to twenty-four hours and succeeded by a corresponding diminution to a level below that previously observed, are signs of a mild and desirable **focal** reaction. A very transient and slight fall in content of opsonin, lysin, agglutinin, anti-toxin, or bactericidin in the serum, followed by a definite increased content in the same, are all evidence of an immunizing response.

If any one or more of these reaction signs are evidenced, our initial dosage may be assumed to have been appropriate to the case, and the usual procedure is to await the first signs of retrogression and then reinoculate with the same dosage.

Should none of these signs be detected within thirty-six to forty-eight hours and the patient's condition remain as before or become worse, reinoculation is to be performed; whether the dosage shall be increased by 50 to 100 per cent. must depend upon the urgency of the case. Personally I am always reluctant to increase a first dose, as this, even in the absence of all signs of reaction, sometimes proves to have acted as a strong stimulus to antibody formation by the apparently unresponsive tissues. If, however, the case is so serious that delay may be fatal, then the bolder policy should be adopted.

In the rare eventuality of a focal or general reaction of undesirable degree ensuing, there is nothing

to do but wait till all signs of reaction have passed away and reinoculate with a dosage of only one-half or even one-quarter the magnitude of the preceding dose, according to the severity of the reaction.

Experience has taught that just as the more acute and more generalized the infection the smaller should be the initial dosage, so also the smaller the initial dosage the shorter the period of time which should elapse between inoculations. Thus cases of septicæmia may require a dose at intervals of 24, 36, 48, or 72 hours, cases of acute pneumonia at intervals of two or three days, while in chronic pneumococcal bronchitis intervals of five to seven days are likely to be appropriate.

Just as retrogression in the clinical signs and symptoms is the signal for reinoculation, so diminution in the focal and general reaction thereby excited is the signal for increased dosage ; increments in dosage are usually made to the extent of 100 per cent. of the preceding dosage.

Simply as the result of experience I have found it wise, as mentioned above for the initial dose, to repeat any given dosage before proceeding to a higher, even if no focal or general reaction be manifest, for a second dose, perhaps after a slightly reduced interval, sometimes excites a definite immunizing response not brought about by the first inoculation with that given dosage. It is also a safe rule that if ever in doubt as to whether an increase should be made in dosage or an inoculation is due to be made, give the patient the benefit of the doubt ; in other words, better an underdose than an overdose, better wait too long than inoculate too soon ; as experience grows so will doubt arise the less frequently, and it will become possible to utilize to the full the laboratory experience already given,

that a few large doses produce a speedier and greater rise in antibodies than many small ones.

The instructions given above may be put into tabular form, assuming that we have to deal with a case of pneumococcal septicæmia, which under our treatment progresses slowly but steadily to a complete cure.

CHAPTER VIII

DISEASES OF THE RESPIRATORY TRACT

ALTHOUGH the successful treatment of respiratory diseases makes the utmost demands upon the time and skill of the immunizer, and these disorders are among the most difficult class of case to bring to a thoroughly satisfactory conclusion, such admirable control of dosage and intervals is furnished by the focal and general reactions, upon which close observation can be kept, that I have thought it wise to consider these cases now in detail, in order that the reader may, by giving them full consideration, become so familiarized with the question of reactions that this knowledge may be assumed in subsequent chapters, and my task of telling him how to use his vaccine to the best advantage in each class of case considerably lightened.

The list of microbes capable of setting up pathological conditions of the respiratory tract is a very large one, even the following one perhaps not being complete: *B. influenzæ*, *Bordet's bacillus*, *B. of Friedländer*, *pneumococcus*, *streptococcus*, *M. catarrhalis*, *M. paratetragenus*, *B. Septus*, comprising the common catarrhal organisms, and possibly a coccoid filter passer, to which have to be added *staphylococcus*, *B. ozænæ*, *B. diphtheriæ*, *Hoffmann's bacillus*, *M. tetragenus*, *B. typhosus*, *B. coli*, *B. proteus*, *B. of rhinoscleroma*, *meningococcus*, *Lepra bacillus*, *B. tuberculosis*, *spirochætes*, and *Streptothrix actinomycosis*.

The 250 large pages of my book on *Bacterial Diseases of Respiration* were inadequate for a full consideration of the subject, so it becomes an obvious necessity to omit much from this small book. I propose therefore to deal fairly fully with some of the more important and common disorders, and leave the treatment of the others to be deduced therefrom by my readers, those I have thus selected being: (1) nasal and postnasal catarrh, pharyngitis, laryngitis ; (2) middle ear disease ; (3) bronchitis ; (4) pneumonia ; (5) lung abscess and bronchiectasis ; (6) asthma ; (7) hay fever ; (8) whooping cough ; (9) tuberculosis ; (10) actinomycosis.

If a success is to be made of the therapeutic immunization of any case, it is essential that the doctor should first ask himself certain questions, of which the following are some of the more important.

(a) Is the bacterial infection a primary cause of the pathological condition, or is it only secondary to some other pre-existing defect or abnormality, in the absence of which no suitable nidus would have existed for the multiplication of the bacteria ? For instance, a perfectly healthy normal nasal mucosa may suddenly, from some unknown cause, have its vitality impaired and resisting power lowered, with the result that stray pneumococci find a resting-place, multiply, and initiate an acute nasal catarrh ; the vitality of the parts improving and their resisting power being raised, the pneumococci find the soil uncongenial and soon die out. On the other hand, abnormalities may exist, a blow on the nose may deflect the septum, and the turbinal bones be so injured that on one side of the nose an excessive airway may exist, on the other a very deficient one, with the result that on one side the air current is never sufficiently warmed, while on the other it becomes more or less completely

obstructed, especially when the mucous membrane becomes from any cause unduly turgid. The mucous membrane may at first remain perfectly healthy, then one day its vitality is lowered and infection by the pneumococcus occurs. This results in increased turgidity of the mucosa, further obstruction to the downward flow of the secretion, stagnation of the parts, and a lowering of the resisting power, from which they seem unable to recover, the result being that the pneumococcal infection becomes chronic and probably extends to the nasopharynx. In our first example natural recovery is almost certain to ensue ; in our second, even with the help of vaccines, the balance may never be restored, unless and until attention is directed to the prime cause of the infection and the deflection of the septum is corrected and the turbinal crests removed. Now this is work for the surgeon, not for a vaccine, yet in numberless instances like this vaccine therapy has been set to perform an impossible task and received the blame for a failure which should never have been experienced. In a similar way it is not fair to set a vaccine to cure a chronic arthritic condition without first calling in a dentist to obliterate the pyorrhœic pockets in the gums, "*vera fons et origo mali*," from which the responsible streptococci are continually making their way into the circulation and perhaps lodging around the joints.

(b) Are the tissues generally in a fit state to respond to any further stimulus, or are they so overladen with toxin as to be incapable of making any further effort at producing antibodies ? In the early stages of pneumonia there is little doubt that much good may accrue from the administration of the right dose of a vaccine of the right strain. Toxæmia is not far advanced, and the tissues are able to respond to the vaccine by the

production of bactericidin, agglutinin, lysin, opsonin, and antitoxin, as has been proved experimentally ; but later, when the tissues are permeated with toxin, they can no longer do this, either to an adequate degree or even at all. Prior neutralization of the circulating endotoxin is a necessity, and in the case of Cole's Type I this can be done by giving a sufficient dose of Type I antitoxic serum ; for Type II a not very satisfactory serum is available ; but for the other types no antiserum has as yet been prepared.

(c) Granted the possibility of increasing the antibodies sufficiently, is it possible to ensure their access to the infected foci, or, as in the case of cerebro-spinal fever, are the bacilli and other toxins at work in a space to which access of the antibodies is denied ? Similarly it is little use raising the blood-content of antibodies to the staphylococcus to great heights if they cannot reach the staphylococci in the dense walls of a closed abscess cavity, where the pressure outwards of the fluid contents is far greater than the inward pressure of the circulating fluids.

Attention to these and many similar questions wherein first principles are involved would save vaccine therapy from being sent on many a hopeless mission, and considerably raise its status as a dependable envoy.

I have so frequently in my writings drawn my readers' attention to these simple elementary principles that it is with feelings of gloomy forebodings for the future of vaccine therapy that I find them continually neglected and overlooked. This omission is, in my opinion, responsible for the major portion of the failures that are laid at the door of this method of treatment. In a book of this compass it is not possible to indicate for every disease the various preliminary considerations to

which the doctor should direct his attention before sending his vaccine on what will otherwise be nothing but a fool's errand ; he should by now realize what a vaccine is, and how it works, and what it can reasonably be expected to accomplish ; let him therefore ensure that a correct diagnosis is made of the infective organism or organisms, best by co-operation with a skilled clinical bacteriologist, procure a properly made vaccine true to strain and type, use it intelligently and with the assurance that the antibodies can freely reach the invaders at the foci of infection, and he will have little cause for disappointment with his results.

(I) **Nasal and Post-nasal Catarrh, Pharyngitis, Laryngitis.**—These several disorders are grouped together, because not only are the infective agents the same, but the first is commonly antecedent to the others. Moreover, the only controls for dosage and intervals are past experience, bacteriological examinations of the secretions, and clinical symptoms ; the more exact methods of control are not available.

The infective agents may be any one or more of the following : *B. influenzæ*, *B. of Friedländer*, *pneumococcus*, *streptococcus*, *M. catarrhalis*, *M. paratetragenus*, *B. septus*, Hoffmann's bacillus. A pure infection by one organism only is quite a rarity ; it may possibly happen with the *pneumococcus*, *B. septus*, and *B. of Friedländer*, but for practical purposes a double or treble infection may be said to be always present, requiring naturally the corresponding mixed vaccine. Thus the *B. influenzæ* is nearly invariably associated with the *pneumococcus*, *streptococcus*, or *M. catarrhalis*, the *pneumococcus* with the *M. catarrhalis*, the *B. septus* with the *M. catarrhalis* or *pneumococcus*, and so on.

Because smears and cultures show ten pneumococci

present for every one *M. catarrhalis* is no reason for excluding the latter from the vaccine, as is so very often done, the result perhaps being that as the pneumococcus disappears, the *M. catarrhalis* not only relatively but absolutely comes to the front. In respiratory infections pre-eminently are mixed or combined vaccines an essential to success.

Acuteness of infection is no contra-indication whatever to the use of a vaccine, in fact the sooner it is used in an attack the better—*infection is strictly localized, and localized to parts not particularly well adapted to the formation of antibodies*; on the other hand, the blood and lymph supply to the parts is good, and antibodies are readily carried to the infected foci. The only unfavourable factor is the fact that the bacilli are frequently to a great extent resident on the very surface of the tissues, and so almost out of reach of antibodies. The use of a suitable vaccine will, however, tend to prevent attempts at penetration and multiplication of the bacilli in the deeper parts; in this way it diminishes the severity and length of the attack, the danger of complications, and the risk of the infection becoming chronic. In recent years I have seen many attacks wholly aborted, and I have never seen a reaction occur of such severity as to upset the patient severely. My firm conviction is that if every case in the recent severe epidemic of the latter part of 1918 had received, at the first signs of infection, an appropriate dose of a vaccine of *B. influenzae*, pneumococcus, streptococcus, and *M. catarrhalis*, and this had been repeated every two to three days, the death-roll would have been reduced to one-tenth of what it was. At the same time I am quite aware of the fact that many of the fatal cases would not and could not have received vaccine treatment suffi-

ently early to have brought about this ideal result, but even if they had received it at the first visit of the doctor, the mortality would have been very much diminished. In my own practice I did not lose one single patient, and the worst complications I had to deal with were hæmorrhages, pyrexia, and discrete patches of bronchopneumonia, usually confined to one upper lobe. These results are fully confirmed by Dr. Wynn's experiences at Birmingham (*Lancet*, December 28th, 1918, p. 874).

The **appropriate initial dosages** of the several organisms in acute attacks of the upper respiratory tract are as follows: *B. influenzæ* 100 millions, *B.* of Friedländer, *B. septus*, Hoffmann's bacillus, pneumococcus, streptococcus, *M. catarrhalis*, *M. paratetragenus* 50 millions. Of the *B. influenzæ*, pneumococcus, and streptococcus an additional 50 per cent. may be added of sensitized bacilli; if sensitized bacilli alone are used, double the dosages I have mentioned may be employed.

Control of Dosages and Intervals.—The best guide to dosage and interval is found in the clinical condition of the patient. Any general reaction, evidenced by slight rise of temperature, accelerated pulse, or malaise, should pass off within eighteen hours, any increase of expectoration or cough within twenty-four hours. This should be rapidly followed by fall of temperature to a lower level than before if any pyrexia were present, by slowing of pulse, increased feeling of well-being, and improvement in the cough. Should this be the train of events, the dose may well be repeated in three days; if no apparent response is made to the first dose in any way, repeat the dose or give a double one in thirty-six hours. If the patient should respond well to the first and second doses as above, continue with the same dosage and intervals until signs of convalescence, then

double the dosage and extend the interval to five days, continuing treatment till finally tenfold the initial dosage is attained and has been repeated at least once at seven-day intervals.

Should the patient, on the contrary, make no response to the vaccine, even when a fourfold or fivefold initial dosage has been attained (*i.e.* the dose at the second increase), and signs of extension to the lower respiratory tract be in evidence, it is urgently necessary that the bacteriology of the condition be subject to review, as it is highly probable that an essential constituent is lacking. For instance, a pneumococcus-*M. catarrhalis* vaccine being in use, infection by the *B. influenzae* may be present; or a *B. influenzae*-*M. catarrhalis* vaccine being in use, pneumococcus or streptococcus will probably be found. This is a very important point indeed, and failure to think of it brings undeserved reproach upon vaccine treatment.

Whenever a case is doing well on a certain dose and certain interval, be chary of interfering with either without a very good reason, and only total failure to respond in any way to a given dosage justifies an increase without a repetition of that dosage. Occasionally an initial dose while producing a minimal reaction yet so sensitizes the tissues that a repetition of the same dosage results in quite a desirable degree of reaction.

In **chronic** infections of the upper respiratory tract, let me once more say, exclude all primary and predisposing causes, have enlarged tonsils and adenoids seen to, and assure yourself that your patient knows how to breathe properly—and if he does not, put him on to simple breathing exercises.

Again the bacteriology is nearly always complex, and however carefully the vaccine is made in the first

place, and the proportion of the several constituents adjusted, watch should always be kept on the invaders. It is more than likely that sooner or later one will come to the front to the exclusion of the others, or a fresh enemy be added to the ranks; in either case a fresh vaccine may be necessary.

Failure in these directions is, in my experience, the commonest cause of failure in the other direction, viz. the cure of the condition.

The initial dosage of the various microbes may be retained at the same level as in the case of an acute infection, for failure on the part of the patient to respond at all will only entail the loss of three days in time, or one may make a start with double the dosages I have indicated, using an interval of five to seven days at the start and of seven to ten days later on. Undue haste in increasing the dosages is to be deprecated, as I think it is likely to increase the chances of missing a fresh invader or the rushing to the front of one of the old ones.

High ultimate dosages, viz. 1,000-2,000 millions *B. influenzae*, and 500-1,000 millions of each of the others, are very often necessary for cure.

Results.—Absolute extinction of all the infective agents from the parts concerned is a consummation to be wished for but practically impossible of fulfilment. Sterility of the upper nasal passages may easily be brought about in most cases, but the other parts are so open to reinfection that even if they were sterilized, they would not long so remain. Again, as a result of long-continued infection of parts probably not anatomically perfect, slight changes are brought about which lead to continual irritation in mild degree of the parts and especially of the secreting cells; hence excess of

mucus is likely to be formed and the very vascular submucosa is liable to become turgid and give rise to slight feelings of discomfort. Thus a perfect cure is by no means easy to bring about, and is not likely to be attained in the majority of cases ; what may reasonably be expected is distinct amelioration of the condition, definite increase of the patient's comfort, and a very greatly diminished liability to exacerbation or attacks of acute catarrh. If this improvement is to be maintained, two short immunizing courses every year should be given, the one beginning about the middle of September, the other at the end of January or middle of February. This procedure has been followed in the case of many scores of my patients with very satisfactory results. I do not say none of them ever catch a cold, but with very few exceptions indeed they say they only catch a very small proportion of what they used to do, that those they do catch are very much milder in type, very seldom incapacitate them or spread to their chest. I have endeavoured to get into touch with as many as I could during the writing of this book ; and of all I have heard from, not one has fallen victim to the prevailing epidemics, four who had not received a complete immunizing course during the preceding six months said they had caught slight head colds, but refused to dignify them with the name of "influenza."

Among the rare forms of chronic nasal catarrh, infection by the Ozæna bacillus may be mentioned. Secondary invaders are nearly always present and require attention. I have treated four such cases, three being cured, the other greatly improved. The initial dosage was 50 millions, the final 1,000 millions.

(2) **Middle-ear disease** is only mentioned here because

in a considerable proportion of cases it probably arises from a prior post-nasal infection via the Eustachian tube. Thus the organisms of post-nasal catarrh are among those commonly found in middle-ear disease ; to them, however, must be added others such as *B. coli*, *B. proteus*, *B. pyocyaneus*, *staphylococci*, *B. diphtheriae*, *B. typhosus*, and *meningococcus*.

Prevention, as always, is by far the best cure, and the maintenance of the post-nasal and pharyngeal spaces of children in a good condition by paying proper attention to adenoids and enlarged tonsils would do much to diminish the frequency of this affection.

However, once it has occurred, the vaccine therapist can only play a modest second rôle to the surgeon's lead, and in cases which do not tend to heal a vaccine can hardly fail to expedite matters. The dosages of the catarrhal organisms will be as given for acute catarrhs, modified with due regard to the patient's age.

With the same proviso, for the other organisms it will be as follows : *B. coli*, *B. proteus*, *B. pyocyaneus*, *B. typhosus*, *B. diphtheriae* 50 millions, *meningococcus* and *staphylococcus* 100 millions. Intervals and subsequent dosages will be controlled by clinical signs and symptoms and bacteriological examinations.

In diseases of the ear new invaders are especially apt to make their appearances and old infections to die out, so that, as a routine, fresh smears and cultures should be examined every two to three weeks.

(3) **Bronchitis.**—In this condition we have the one above all where vaccine treatment has full scope and every possible chance. The nature of the infection can be determined with accuracy, the antibodies have free access, and every possible means for controlling dosages and intervals is at our disposal. Focal and general

reactions can be excited at will, and close observation kept in local conditions with the aid of the stethoscope. The one thing which militates against success is again the fact that the bacteria are resident on the surface and not in the tissues.

Infective Agents.—The bacteria commonly concerned in the causation of bronchitis are *B. influenzæ*, pneumococcus, streptococcus, *M. catarrhalis*, and less frequently *B. of Friedländer*, *B. proteus*, *M. paratetragenus*, and very rarely indeed *B. septus* or some other diphtheroid organism. Although at present not amenable to vaccine treatment, for the sake of completeness I here mention a form of hæmorrhagic bronchitis first described by Castellani (*Lancet*, 1906, p. 1384) as occurring in Ceylon. It has since been detected in France among the native troops coming from the Far East by Violle (*Lancet*, December 7th, 1918, p. 775). It is most likely to be mistaken for pulmonary tuberculosis, but is easily differentiated by the vast numbers of spirochætes voided in the sputum. The first four on our list are in varied combinations responsible for well over 95 per cent. of all cases of both acute and chronic bronchitis.

Dosages.—The initial doses are precisely those given in the case of acute nasal catarrhs, viz. 100 millions *B. influenzæ* and 50 millions of each of the others ; if, however, the general condition of the patient be bad and the doctor be anxious to avoid any possible general reaction, these initial dosages may be reduced to one-half. If the patient fail to make any response to this diminished dose, it need not entail more than the loss of two days. At the same time I have never seen the slightest ill-effect ensue from the dosages recommended.

Control of Dosages and Intervals.—Firstly a four-

hourly temperature and pulse chart should be carefully kept, and the sputum voided from 8 a.m. to 2 p.m., from 2 p.m. to 8 p.m., and from 8 p.m. to 8 a.m. collected and measured. These records should be available for twenty-four hours prior to the administration of a vaccine if possible. This can be easily done if the doctor awaits the preparation of an autogenous vaccine. If he is contemplating the use of a stock vaccine, he should at once give instructions for these observations to be made, and inasmuch as vaccine is by far the best agent we possess for the treatment of bronchitis acute or chronic, every doctor should make a practice in ordering this routine for all his cases as soon as he diagnoses the complaint. His next step is to make careful stethoscopic examinations of the chest, and chart his observations on the convenient forms¹ seen on pp. 132-8.

Thus, prior to giving the vaccine the doctor knows what course the P. and T. are taking, the amount of expectoration, and has a very good idea of the clinical signs in the chest, how they are varying, and what course they are likely to take. He is now going to give a vaccine in such a dosage that he hopes it will produce a general reaction just noticeable on the P. and T. chart, and such a focal reaction as will easily be discernible with the aid of the stethoscope and be further indicated by changes in the amount of sputum. These reactions should be at their height between the sixth and twelfth hours, rapidly pass off, and be succeeded by definite improvement in each particular somewhere between the twelfth and twenty-fourth hours. He will therefore choose such a time for the performance of the inoculation as will enable him to re-examine the patient without fear of having missed the all-important focal

¹ These charts are obtainable from H. K. Lewis & Co, Ltd.

reaction. Obviously, the best time, then, for the inoculation will be in the forenoon—say at 10 a.m. He will then re-examine somewhere between 4 and 8 p.m. with the reasonable hope of detecting any focal reaction which may have occurred. If no signs of this present themselves, he will return later, if possible, for the information thus derived from the first two or three doses is simply invaluable in the conduct of any important or difficult case. Another visit at 10-12 a.m. next day will enable him to judge the rapidity with which the negative phase of the reaction has passed off, and the kind of immunizing response the patient is making to the inoculation.

Charts I-VII, pp. 132-8, illustrate the changes produced in a case of mine of chronic bronchitis, where the changes are more definite and easier to observe, inasmuch as once one is familiar with a case, little room is left for doubt as to the precise changes brought about by the vaccine; whereas in acute cases it is of course much more difficult to decide in one's own mind what precise changes would have occurred apart from the vaccine. This difficulty is, however, minimized by the P. and T. chart and sputum measurements.

As delayed reactions sometimes occur, he should always wait for thirty-six hours before deciding that no reaction is likely to occur. If after thirty-six hours nothing has happened, and the loss of another twenty-four hours is not likely to be a serious matter, he should reinoculate with the same dosage, otherwise employing double the preceding one.

Subsequently, such close observations are required only after increased dosages, the precise effects of which the doctor is anxious to estimate.

Results.—Those who are at all familiar with the

results of vaccine treatment in acute bronchitis when such dosages as I have advised are employed are unanimous in their belief that the treatment (*a*) is devoid of all danger; (*b*) conduces to the more rapid recovery of the patient; (*c*) considerably reduces the risk of complications and especially of pneumonia, and, as far as one can judge, diminishes the risk of chronicity. With the absurdly small and ill-adjusted dosages advised by one or two bacteriologists these results are hardly to be expected; a more extensive bedside experience would probably have prevented their falling into such mistakes as they have made.

During the severe epidemic of 1918 I subjected all my cases (with the exception of a certain serial number that I treated with intravenous injections of *ol. alii* dissolved in equal parts of alcohol and ether) to vaccine treatment, beginning as early in the attack as possible, and never employing a smaller initial dose than 50 millions each of pneumococcus, streptococcus, and *M. catarrhalis*, and 100 millions *B. influenzae*. In not one single case did a patient have a reaction, local or constitutional, which was upsetting in the least degree; not one patient developed lobar pneumonia, and not one died out of a total of ninety-seven cases. At least 20 per cent. of these might have been described as seriously ill when first seen; several had had repeated haemorrhages, rigors, vomiting, and a temperature of over 103° F.; and looked very anxious and of a dusky hue which I am accustomed to regard as a grave symptom. Most of these cases had patches of broncho-pneumonia, much the more often in the upper lobes, but sometimes in the lower also; in none of them did fresh patches appear to develop after the first inoculation, and in only one case which is possibly complicated with apical phthisis

did the temperature fail to drop to normal after the second or third inoculation. Cases in which the temperature hovered around 100° F. at the beginning seemed to make the slowest recoveries. My results are completely paralleled by those of W. H. Wynn (*Lancet*, December 28th, 1918, p. 874), whose dosages much resembled my own, except that his initial dose of *B. influenzae* was only 30 millions. He states that some hundreds of cases were treated on these lines by himself and by practitioners associated with him, and that of the cases directly under his own care there was only one death among those inoculated within forty-eight hours of the onset ; some of his cases were of extreme severity and very grave prognosis when first seen, yet made good recoveries. He tells of 17 patients from the same community, 9 of which had broncho-pneumonia ; 5 of these were not under his care and not inoculated, and of these 4 died, the other 4 he inoculated and all survived. He also gives a short account of 3 cases of very severe confluent broncho-pneumonia, all of which made speedy recoveries after inoculation. The youngest case was in a baby of 12 months with well-marked broncho-pneumonia ; 38 hours after receiving 15 millions of each organism she was sitting up and playing. In conclusion, he advocates the use of larger doses than he has actually given, and falls practically into line with the dosages I have been urging on the profession for the past ten years.

Several other observers have recorded their results in much smaller numbers of cases than those of Wynn and myself, but so far as they go completely confirm our results, and even the most prejudiced cannot fail to admit that coincidence will hardly suffice to account for the very great difference between the results obtained

by those doctors who, having had considerable prior clinical experience of vaccines, have inoculated the patients during 1918 and those obtained on general lines by doctors who have not used vaccines. For instance, compare the results given above with what occurred at St. Peter's Home, Clapham, where 50 inmates out of a total of 280 are stated to have died of "influenza" during the late epidemic.

In chronic bronchitis the results that may be confidently expected are :

(a) Complete cure or very great improvement of the chronic condition, with diminished expectoration and cough, increased freedom of breathing, and general improvement in health ; frequently patients put on 14-21 lb. in weight during a course of treatment. The factor that mainly influences the prognosis is the degree of emphysema associated with the bronchitis. Advanced emphysema tells very heavily against the chance of complete cure ; the anatomical changes have not only reduced the vitality of the parts, but conduce to stagnation of the secretion and multiplication of the germs. Strange to say, the cases that do worst are those in which one of the associated organisms is *B. coli* or *B. proteus* ; they do worse even than the cases of chronic infection in which *B. influenzae* is the chief invader.

(b) Great diminution in the frequency of exacerbations and in the severity of such acute attacks as do supervene. Instead of continually getting acute attacks which clear up slowly, many patients only incur two or three mild attacks which do not actually necessitate their taking to bed, although this course is always much to be recommended. Of all my chronic bronchitis cases, not one incurred a severe attack during the epidemic of 1918.

(4) **Pneumonia.**—In pneumonia we come to a disease

of quite another class. At a certain stage in quite a fair proportion of cases, if not in all, it partakes of a septicæmic nature ; a little later the pulmonary tissues are deeply invaded by bacteria readily accessible to any circulating antibodies, which unfortunately at that stage are almost totally absent ; yet a little later antibodies are circulating freely but are almost totally denied access to the invaders ; yet later and as a rule finally the antibodies are available, and they can get free access to the bacteria. In exceptional cases resolution is delayed and patches of consolidation may persist. It will thus be seen that there is a period in pneumonia when an artificially produced increase in the circulating antibodies may be of the very greatest value ; the difficulty is that only rarely is the vaccine given at the period when it can do the most good.

All parts of the lungs are, however, but rarely in the same stage, so that if the vaccine is too late to be of service to one part of the lungs, it may yet be of avail with regard to another part ; unfortunately, however, by this time the tissues are so overladen with endotoxin against which they are striving their utmost to elaborate antitoxin that it must be a matter for doubt both as to the wisdom of diverting their attention from the matter in hand and as to whether they are capable of responding to any further stimulus differing but slightly perhaps in nature from that afforded by the infecting bacteria. Obviously the prime necessity is the wherewithal to neutralize the powerful endotoxin. If the pneumococcus be of Type I, a simple matter to determine if the antisera of the various types be available, then the new antiserum of the Rockefeller Institute is the agency required, and, as clinical records show, one upon which considerable reliance can

be placed. The best treatment at that stage is to give 50-100 c.c. of this serum, and repeat at each subsequent rise in temperature; vaccine treatment being reserved for later, as for instance if relapse threaten or convalescence be delayed and patches of consolidation persist. But if the microbe be of any other type than Type I, no antiserum of value is as yet available, and it may be worth while to give an autogenous vaccine a trial, and considerable preference is being given to a sensitized vaccine. As, however, I have pointed out, the right time to use a vaccine in pneumonia is in the early stages, before consolidation has at all advanced and before toxin has been liberated in any great degree; for while antitoxin only neutralizes toxin, vaccine gives rise to other necessary antibodies as well, *i.e.* to bactericidin, lysin, opsonin, and agglutinin, all of value in the extinction of the infection.

The correct application of specific therapy to cases of lobar pneumonia may thus be summarized:

Stage of the Pneumonia.	Correct Treatment.
1st stage, little consolidation, no toxæmia	Vaccine, preferably sensitized or mixed
2nd stage, advanced consolidation, marked toxæmia	Rockefeller antitoxin, if Strain I; if another strain, sensitized vaccine
3rd stage, resolution and slight toxæmia	Continue antiserum, but also give vaccine
Delayed resolution	Vaccine

Initial Dosage.—If an unsensitized vaccine be employed, begin with 50 millions; if a sensitized vaccine be available, either add 25 millions to the 50 millions unsensitized or give 100 millions of the sensitized.

Control of Dosages and Intervals.—This will mainly

be by means of the P. and T. chart, and the general clinical condition of the patient. Stethoscopic observations may help, but are hard to interpret aright, as no clinician, however skilful, can predict even to himself the probable condition of the chest twelve or twenty-four hours subsequently. If the dose of vaccine given appears to have excited a transient focal and general reaction, followed in twelve to twenty-four hours by a definite steadyng of the pulse and temperature and apparent improvement in the general condition, the dosage may be assumed to be appropriate. It is hardly wise to await even the first signs of retrogression, but is better practice to reinoculate with the same dose in forty-eight to sixty hours, and so long as the patient seems to be steadily improving I do not favour any change, either in dosage or interval. If, however, owing to the massive nature of the infection, each subsequent response seems to be growing less, either shorten the interval by twelve to twenty-four hours or double the dosage. Serum if available will of course be also given as toxæmia develops. As resolution progresses, the dosages may be materially and steadily increased, and the intervals lengthened to three, four, or five days.

If, however, no apparent response is made to the initial dose, repeat in twenty-four to thirty-six hours; if still no response, give a double dosage twenty-four hours after the second, and so on, until a response is made or it is decided that vaccine is of no avail.

If the patient respond too strongly to the initial dose, and this may rarely happen, wait till all signs of the reaction have passed away and begin again with 25 or even 10 millions, according to the degree of reaction.

In cases of delayed resolution an initial dosage of 50 millions is appropriate. Additional help in control

of dosage and interval is afforded in these cases by stethoscopic observations, as fluctuation in the clinical signs is hardly likely to occur naturally from day to day.

Results.—No really reliable statistics are available. Opponents of vaccine treatment are inclined to accept only such statistics as are based on series of consecutive cases. Those who know when and how to use vaccines are hardly ever likely to be in a position to afford such information, as they are not likely ever to adopt such an ill-judged course as to submit every case of pneumonia to vaccine treatment. Careful selection of appropriate cases should always be made, and every patient infected by Type I pneumococcus—and these are those in whom the mortality rate is highest—should receive the benefit of Type I antiserum as soon as symptoms of toxæmia develop. No physician has the right to play about with cases of pneumonia to satisfy statisticians or opponents of vaccine treatment. It thus becomes necessary to rely on the clinical impressions of reliable observers.

I think it may fairly be stated that among those who have used the initial dosage I advise, and excluding those who toy with vaccines, giving only half, one, two, or even five millions, the general opinion is that (*a*) they have never seen vaccine do harm; (*b*) they have certainly seen it do good; (*c*) apparent good results in the majority of cases; (*d*) complications are minimized; (*e*) convalescence hastened.

More than this it is hardly discreet to urge. For unresolved pneumonia I think it may fairly be said that in vaccine we have a reliable and certain remedy. I myself have never failed to cure a case, with the sole exception that a small focus occasionally persists in the site I have already indicated, viz. in the area between

the fifth and seventh ribs, and usually somewhere between 1 inch internal to the nipple and 2-3 inches external to it. Sometimes this area is as big as a six-penny piece, sometimes as large as half a crown. As already stated, I believe this area of infection to be, not a sequel of the pneumonia, but precedent to and the direct cause of it.

Finally, I would remind my readers that mixed infection is quite common in pneumonia, *B. influenzae*, streptococcus, or *M. catarrhalis* being frequently associated with the pneumococcus. If the best results are to be got out of the vaccine treatment, the associated microbe or microbes must be included in the vaccine. The mixed infection is especially likely to make itself felt after resolution has begun.

Broncho-pneumonia.—In this disease the conditions are more favourable to vaccine treatment than in lobar pneumonia, inasmuch as from the nature of the lesions the antibodies have better access to the infected foci. At the same time the bacteria capable of initiating the disease are much more varied than is usually the case with lobar pneumonia, and mixed infections are even more common. This obviously necessitates a thorough bacteriological diagnosis being made, and extreme care being devoted to the preparation of the vaccine lest some important ingredient be omitted.

In my experience the results are fully up to expectation. The spread of the infection is rapidly controlled, the pulse and temperature steadied, general conditions improved, toxæmia limited, and convalescence rapidly brought about.

Children appear to do exceptionally well and make good and rapid response to relatively high dosages. For instance, for an infant 1 year old 3 millions of pneu-

mococcus or *B.* of Friedländer will not be found excessive; to one between 1 and 3 years, 5 millions; to one between 3 and 7 years, 10 millions; to one between 7 and 14 years, 25 millions may be safely given. With a sensitized vaccine I do not think any alteration in the initial dosage should be made; dosages and intervals are to be controlled in the usual way.

(5) **Lung Abscess and Bronchiectasis.**—Anatomical considerations will at once indicate that vaccine treatment has a tough task in front of it in dealing with these cases. Drainage of the secretion is such a difficult matter that stagnation inevitably leads sooner or later to invasion by bacteria with marked proteolytic powers. Sometimes these are anaerobic putrefactive bacteria, and against these vaccine does not seem to be effective. Experience of these cases is also so limited that the best procedure is difficult to determine.

I have had four cases of the kind—three the sequel of pneumonia, the fourth also the sequel of pneumonia but in a tuberculous subject. Of these four cases I succeeded in curing three after twelve to eighteen months' treatment: two are alive and well to-day after five and seven years; the tuberculous one remained well for several years, then died of pneumonia following on influenza. The fourth case I nearly succeeded in curing, but unfortunately tried in turn intravenous injections of iodoform and nascent iodine treatment via the stomach, in each instance with immediately disastrous results, the patient relapsing badly; from the second relapse she made little progress, lost weight and spirits, and finally died. I am firmly of the belief that if I had relied solely on vaccine, cure would ultimately have taken place. The infective agents are the common catarrhal organisms with the addition of

staphylococci, *B. coli*, *B. proteus* group, and various anaerobes.

(6) **Asthma.**—Inasmuch as bacteria are certainly not the true cause of asthma, but merely in certain cases the toxic agents which induce the manifestation of the true ætiological factor, the best that can be expected from vaccines in asthma is that in a certain percentage of cases they will do good; in a few cases they may even apparently lead to the disappearance of attacks; in a greater percentage they will reduce their frequency and severity; in others they will quite fail to do any good. This, the result of my clinical experience, is precisely what one would expect on “*a priori*” reasoning.

Organisms Concerned.—The commonest bacterium concerned in asthma is the streptococcus group, three varieties being especially common, *i.e.* a very long chained form, the *Streptococcus maximus*, and a very haemophytic long chained Gram-negative form. (For the bacteria of asthma see *Bacterial Diseases of Respiration*, p. 52.)

Next in order of frequency are *M. catarrhalis*, pneumococcus, *B. influenzae*, other bacteria being quite infrequent. That these microbes are concerned in the production of the asthmatic attacks of certain individuals is indubitable, for I can produce a number of patients, a few cured and remaining well for years by the use of the corresponding vaccine, others improved but always capable of responding to a dose of vaccine within twelve hours by a definite mild attack of asthma.

The **initial dosages** are those given for acute nasal catarrh or bronchitis.

The control of dosage and interval is by frequency of attacks, stethoscopic observations, general reactions

and focal ones as evidenced by an ensuing mild attack. Treatment is usually prolonged, and high ultimate dosages, even to 1,000–2,000 millions, are necessary to ensure good immunity. Short prophylactic courses every six months are always advisable in those cases which do derive any benefit.

As it is impossible to forecast whether a case is likely to derive benefit or not, it is always worth while giving a vaccine a trial in this distressing malady; it is not worth while persisting in it if the patient does not derive any benefit in two to three months or fails to evidence a response to the vaccine by having the aforesaid mild attack eight to twelve hours after a dose of vaccine.

(7) **Hay Fever.**—Although bacteria are only very rarely, if at all, concerned in this affection, the toxins contained in the pollen of various grasses and flowers being the common cause, the disease is included here as the treatment is identically the same as if the vaccine were compounded of bacteria.

The source of the toxin varies in different parts of the world; in Great Britain it is usually contained in the pollen of *Phleum pratense* and of rye grass. An ophthalmic test as described on p. 113 will always afford the information whether the toxin contained in our vaccine is really the toxin which causes the disease in that particular patient. Formerly this test was also taken to be a measure of the appropriate initial immunizing dose; accumulated experience points strongly in the direction that much higher initial prophylactic doses are advisable. In treatment, however, it is by no means a bad guide, the initial dose being one-sixth of a c.c. of that strength to which the ocular conjunctiva reacted. Should this initial dosage not cause a very

mild and transient exacerbation in the first few hours or in its absence lead to some clinical improvement, it is an easy matter to proceed to higher dosages. If a conjunctival test cannot be carried out, an initial dose of 25 units may be safely used.

Control of Dosage and Intervals.—As usual the best criterion of effective dosage lies in the production of a very mild reaction; if there be slight exacerbation of symptoms in three to eight hours, rapidly passing off and being succeeded by general amelioration, it may be safely deduced that that dosage is an effective one and no increase is indicated. At the first definite signs of retrogression, which usually appear in two to four days, reinoculation should be performed.

In the absence of any focal reaction, clinical improvement is indicative of adequate dosage but bordering on the inadequate, and on the next occasion a 50 per cent. increase may be made; some administrators may prefer to rest content with that dosage, but shorten the interval to not more than two clear days. If possible in this distressing complaint, it is well to forestall the first definite signs of retrogression, and to reinoculate on the day preceding that upon which reappearance of the symptoms is to be expected. In some cases this may necessitate daily administration of the vaccine, but patients will probably prefer this course to the trial of higher dosages, which may result in the production of a marked reaction and considerable distress.

Results are variable: sometimes extremely good, so that the attack is soon aborted for that season; sometimes very poor, the patient making little improvement, despite the fact that a definite reaction has been made to the ophthalmic test during the winter season. In these cases I cannot but feel that the failure is due to

the vaccine being incomplete or ill-adapted to the patient ; he may be susceptible to the toxins used in the test, but these are not the agents at work at the given time. Yet another percentage of cases get relief to a greater or less extent, and these perhaps constitute the greater proportion of cases.

(8) **Whooping Cough.**—Much of the work on the vaccine therapeutics of whooping cough has been vitiated, as the observers have themselves confessed, by two serious omissions : (1) to realize that whooping cough in well over 90 per cent. of cases is a mixed infection of Bordet's bacillus, *B. influenzae*, and pneumococcus ; (2) to employ adequate dosages.

The omission of *B. influenzae* and pneumococcus from the prophylactic vaccine is not nearly so serious a matter as it is in treatment, for in the former case if adequate immunity be established against Bordet's bacillus, obviously whooping cough will not be contracted, whereas the stamping out of the infection by Bordet's bacillus during an attack is not only rendered more difficult by the omission to deal with the *B. influenzae* and pneumococcus, but even if achieved, only relieves the sufferer from some of the symptoms, and has but little influence upon the liability to complications. It thus follows that to the bulk of the work done no real value is to be attached. The facts I have mentioned—not for the first time in my writings—are now being better realized, and considerably improved results are to be expected in the future.

In view of the very high percentages of cases wherein the infection is a treble one by the bacteria mentioned, I would strongly advise that for therapeutic purposes no vaccine other than the mixed one be employed ; if an autogenous one is to be used, care should be taken

that the work is entrusted only to a bacteriologist of undeniable skill, for it is no easy matter to differentiate *B. influenzæ* and Bordet's bacillus, and the majority of bacteriologists have probably never even seen the latter growing in artificial cultures, for the preparation of which quite special media are an absolute necessity.

Initial dosages (in millions) may be tabulated thus :

Age.	B. Bordet.	B. influenzæ.	Pneumococcus.
Under 1 year .	. 25	10	2
1-2 years .	. 50	25	5
2-3 years .	. 100	50	5
3-7 years .	. 100	50	10
Over 7 years .	. 100-250	100	10-25

As regards the substantially lower dosages employed by some, I am inclined to say, "Spare the child the needle, and put the vaccine down the sink." Subsequent dosages and intervals are to be controlled by the clinical signs and symptoms, but as a rule reinoculation is advisable every second or third day.

Results.—For several years a large orphanage in the Midlands was subject to severe yearly epidemics, and most excellent results were obtained on these lines. Subsequently it was decided to employ prophylactic measures with all the inmates, the result being that the yearly epidemics are a matter of the past. Shaw's experience (*American Journal of Obstetrics*, 1917) has not been quite as favourable as my own, despite the fact that he used full doses of polyvalent vaccine. He concludes that the vaccines are harmless, and do not produce severe reactions, but that the results in the treatment of cases already in the paroxysmal stages are not so striking as in prophylaxis, and the consensus of opinion is that where the proper vaccine is used there is a shorten-

ing of the paroxysmal stage with a reduction in the number and severity of the paroxysms. Whether his inferior results are due to lack of adequate dosages of *B. influenzae* and *pneumococcus* I cannot tell.

Chronic Whooping Cough.—I have had two interesting cases of chronic whooping cough of several years' duration, one in a boy of fifteen, the other in an adult. In both instances I isolated the bacillus from tonsillar swabs along with pneumococci, streptococci, and *M. catarrhalis*. In each case complete cure speedily resulted, the final dosages being 2,000 millions of Bordet's bacillus and 1,000 millions of each of the others.

(9) **Tuberculosis.**—I am afraid I can hardly discuss the "pros" and "cons" of tuberculin treatment as summarily as a recent young writer on vaccines, who, after devoting three small pages to discussing Koch's claims and experiments and none to clinical evidence, concludes that he has said enough to show that the therapeutic use of tuberculins is neither justified by use nor does the experimental evidence on which it is based bear repetition, etc. It is a vast subject, and men of undoubted brains, skill, and honesty differ greatly as to the value of tuberculin treatment. Feeling that the ideal tuberculin had not yet been prepared, I devoted five years to the question, and finally elaborated a preparation which I think is the best available, in that it appears to be devoid of all toxicity and yet is certainly capable of exciting immunizing responses.

There is no doubt that many ingenious theories have led to the almost endless multiplication of preparations, and that for all practical purposes their numbers might well be reduced to half a dozen—*i.e.* Old Tuberculin, Bacillary Emulsion, Albumose-free Tuberculin, Bera-neck's Tuberculin, Von Ruck's Watery Extract, and

T.R. or my own preparation, which naturally I think to be the best ; at all events, chronic cases, treated with it and no other measures besides those which had failed to bring about cure in ten to twenty years, have made complete recoveries so far as tubercle bacilli in the sputum are concerned.

For a reasonably full discussion of the specific therapy of tuberculosis I must refer my readers to *Bacterial Diseases of Respiration*, wherein I lay great stress upon the prime importance of dealing with the mixed infection : this constitutes by far the most important part of the vaccine treatment of the tuberculous. To attack the T.B. with tuberculin and ignore the accessory invaders—I do not say *secondary* invaders, because I believe in the majority of cases they precede the T.B.—is entirely putting the cart before the horse.

The most common complicating microbes are, in order of frequency: streptococcus, M: catarrhalis, pneumococcus, staphylococci, M. paratetragenus, B. influenzae, B. proteus, etc. The dosages and intervals and control of these are precisely those laid down and described in detail in the section devoted to bronchitis, and need no further discussion. Tuberculin treatment may be conducted simultaneously, but this procedure is not wise, as it interferes with the proper study of the reactions induced by the vaccine ; better is it to complete the course with the vaccine, and then go on to tuberculin.

Choice of Tuberculin.—The best tuberculin, in my opinion, must be an albumose-free preparation of the products of the growth of the bacillus combined with certain constituents of the protoplasm of the bacillus. Martindale's Tuberculin "M." is a polyvalent one of this nature, and may be described, but somewhat inaccurately, as a blend of T.R. and albumose-free

tuberculin ; so that if this preparation is not available or does not appeal to the taste of the reader, my advice is, mix these other two in equal proportions and employ the mixture.

The appropriate initial dosages of this cannot be given in the usual off-hand manner of a decimal point : so many cyphers and a 1 : this, and a stereotyped scheme of progressive doses has been always the curse of tuberculin therapy—it is not applicable to one single case, and therefore certainly not to all. Having commenced treatment with a low initial dose, there is one way and one way only in which to arrive at the appropriate subsequent dosages and intervals, which is the way I have already described in full under Bronchitis, *i.e.* by the most careful production of focal and general reactions, their close observation with the stethoscope, and by clinical symptoms generally. Controlled in this manner, as is done in not one case per 1,000, tuberculin is given a real chance, and may benefit a patient, and may even cure him ; at least in a percentage of cases it will certainly bring about the permanent disappearance of the tubercle bacillus.

Once this desirable end has been achieved, it is necessary to maintain the patient's resisting powers to the catarrhal organisms generally and the associated microbes in his case in particular, as nothing is so conducive to the reappearance of tubercle bacilli in the sputum as an acute catarrhal attack of the pulmonary tissues.

The cases which do best, in my experience, are those complicated by the pneumococcus or streptococcus ; staphylococcal cases do not do so well ; and when the *B. influenzae* is constantly present the prognosis is much more gloomy.

(10) **Actinomycosis** is considered here, despite the fact

that this organism attacks other parts of the body with greater frequency, because actinomycosis of the lungs is much commoner, at least in some countries, than is commonly imagined.

The total number of cases recorded of actinomycosis of the various parts treated with vaccine remains small (I have records of only fifteen), but the results are exceptionally good. The largest series of cases is that of Kinnicutt and Mitter (*Boston Med. and Surg. Journ.*, July 18th, 1912, p. 90); they record four cervico-facial, two pulmonary, and two abdominal. Malcolm (*B.M.J.*, October 7th, 1916, p. 488), Collie (*B.M.J.*, May 10th, 1913), Wynn (*B.M.J.*, March 7th, 1908), and Dean (*Lancet*, 1917, vol. i. p. 82) record four most successful cases, two of which were severe thoracic infections. The vaccine is difficult to prepare, and impossible to standardize accurately by any other method than weighing, which has not been done except by Wynn. The growth has been fragmented as much as possible and the fragments counted when standardization has been attempted. Wynn's dose was 0.001 milligram of dried bacterial substance, with the result that the pulmonary abscess was ultimately cured. In the other cases the dosage has varied from $2\frac{1}{2}$ to 25 million fragments, over-dosage being indicated by excessive focal reactions. Of the five pulmonary cases on record, three were ultimately cured; treatment may, however, be necessarily protracted.

CHAPTER IX .

DISEASES OF THE CIRCULATORY SYSTEM

Disease.	Associated organisms.
1. Septicæmia and pyæmia .	Streptococcus, pneumococcus, staphylococcus, gonococcus, <i>B. coli</i> , <i>B. typhosus</i> , Shiga's bacillus, <i>B. pyocyaneus</i> , <i>B. proteus</i> , <i>M. tetragenus</i> , etc.
2. Endocarditis	Streptococcus, pneumococcus, staphylococcus, <i>B. influenzae</i> , gonococcus, <i>B. tuberculosis</i> , etc.
3. Adenitis and lymphangitis	As for endocarditis
4. Cerebro spinal meningitis.	Meningococcus, pneumococcus, streptococcus, <i>B. coli</i> , <i>B. typhosus</i> , <i>B. influenzae</i> , <i>leptothrix</i> , and <i>B. tuberculosis</i>
5. Acute rheumatic fever .	Streptococcus <i>rheumaticus</i>
6. Malta fever	<i>M. melitensis</i> and <i>M. paramelitensis</i>
7. Plague	<i>B. pestis</i>
8. Scarlet fever	Streptococcus <i>conglomeratus</i>
9. Rabies	Unknown

(I) **Septicæmia and Pyæmia.**—Unless we rigidly confine our definition of these diseases to cases wherein the bacteria are multiplying in the blood-stream, many diseases, such as typhoid fever, pneumonia, influenza, etc., would, at some period of their course, fall within this category. About no other class of bacterial infection are such diametrically opposed views held with regard to the value of vaccine treatment as with regard to septicæmia.

Some like myself, who have never lost a case of septicæmia, no matter how desperate the condition, naturally hold a very optimistic view; others, who have experienced many failures, are naturally equally pessimistic; and the explanation of these divergent opinions is not easy to find. Sometimes faulty bacteriological work is undoubtedly at the bottom of it, as for instance in a case about which I have only this week received a letter. A week after childbirth a lady developed pyuria and then septicæmia; the urine was examined, and of course found to be swarming with *B. coli*; without any more ado and without any blood culture being made, the diagnosis of septicæmia due to *B. coli* was considered as established. Now, as all of us with any amount of experience fully know, a pure infection by *B. coli* in a case such as this is rare enough almost to be worthy of the description "unknown." Streptococci or staphylococci are almost invariably associated with the *B. coli*, and the detection and isolation of the two former when vastly outnumbered by *B. coli* is only easy when quite special methods are adopted. Vaccine treatment of this case along the intended lines can only end in failure.

Well enough I know, however, that such an explanation as this only accounts for a certain percentage of failures. The major portion, I think, are due to failure to realize that septicæmia is almost invariably due to bacilli escaping into the blood-stream from an infected focus elsewhere, and consequent failure to devote adequate attention to the cutting off the further egress of bacteria from that focus or those foci, which usually entails some operative procedure. On several occasions I have been able to diagnose the presence of undiscovered foci from the nature of the reaction to my vaccine; each

time the well-known surgeon laughed at me, and was positive he had dealt with all such foci, but in each cast subsequent events confirmed my view. For instance, a rigor or rigors following on the administration of what my experience tells me is a perfectly safe and appropriate dose for the condition is practically pathognomonic of pus under pressure.

Another proportion of the failures is probably due to lack of attention to the production of reaction leading to the use of ill-judged dosages and intervals.

Only when all localized foci of infection have been indubitably dealt with by the surgeon and the patient's tissues nevertheless remain overloaded with toxin, two conditions which are rarely compatible the one with the other, do I consider a case too far gone or ill-adapted for vaccine treatment, and even then a reliable appropriate serum may pave the way for vaccine.

To ensure good results in septicæmia the essentials, then, are: (a) adequate attention by the surgeon to all localized foci of infection; (b) thorough measures for the elimination of toxins and the neutralization if possible of what fails to be eliminated; (c) a thorough and complete bacteriological diagnosis, as established by blood-cultures, direct examination and cultures of material from each and every infected focus; (d) the employment of a complete vaccine from which no essential element has been omitted; (e) full utilization of the control afforded to dosage and intervals by the reactions produced; (f) the production of such reactions without which we may be almost certain that inadequate dosages are being employed or that from the vaccine some essential constituent has been omitted.

I must honestly say that I have never read the description of a failure wherein I have been satisfied that due

regard has been paid to all these essentials. I will readily admit that it may at times be impossible to comply with all these conditions, but if then failure result, it is not a failure which rightly should be attributed to vaccine treatment, but to the lack of opportunity afforded to those concerned or to lack of care and skill in utilizing their opportunities.

A good example of what I mean is afforded by the description of a case of subacute infective endocarditis by Bernard Hudson (*B.M.J.*, November 9th, 1918, p. 512), wherein he states: "For treatment, courses of antistreptococcal serum and also vaccines were tried, *but with no effect whatever.*" I can imagine a serum rightly used even producing no effect whatever, but of no vaccine rightly used can this be said. A vaccine must be so used that it does produce *an effect*, even if this effect does not ultimately prove to the patient's advantage; until some sort of reaction has been obtained an effective dosage has not been attained.

It will have been gathered that, as always, I attach importance to the use of such dosages only as are productive of reactions, focal and general, and this is the case. If reactions cannot be produced, then we know the tissues are not making an adequate immunizing response, whether the failure be on their shoulders or on our own. With free drainage of the infected foci it is no easy matter to produce an excessive general reaction, nevertheless I hold with the majority of workers, and quite possibly wrongly, that small stimuli oft repeated are more applicable to cases of septicæmia than large infrequent stimuli. Accordingly the **initial dosage** for unsensitized vaccines I advise of each organism is 5 millions for Shiga's bacillus, *M. tetragenus*, 10 millions for streptococcus, pneumococcus, gonococcus,

B. coli, *B. proteus*, *B. pyocyaneus*, 25 millions *B. typhosus* and *B. influenzæ*, and 25–50 millions *staphylococcus*. If a sensitized vaccine be available, double or even quadruple these dosages may be employed. An excessive general reaction to these initial dosages being surely due to the presence of pus under pressure, in the event of such an occurrence the diagnosis may be safely made of a focus which needs surgical attention. The control of subsequent dosages and intervals lies in the general reaction as manifested by the temperature and pulse chart and the general clinical condition of the patient. At the beginning, and until one has become familiar with the responsive powers of the patient's tissues, it is perhaps wise to await the first signs of retrogression before reinoculating; later, and when this knowledge has been acquired it is much better practice to endeavour to forestall the slightest relapse on the part of the patient. Several successful cases are recorded in *Vaccine Therapy, The Journal of Vaccine Therapy*, vol. i. No. 9, p. 239, and *The Lancet*, September 11th, 1909, p. 780.

(2) From what I have already said, it will be understood that vaccines are seriously handicapped in the treatment of **endocarditis** owing to the fact that here an important focus of infection cannot be dealt with surgically. None the less a few successes are on record where the infective agent has been the streptococcus (see also *Acute Rheumatic Fever*, p. 184) or *staphylococcus*. Cases due to the *B. influenzæ* treated with vaccine have all died, but I am not at all satisfied that adequate dosages were employed in a single recorded case. I have never had a case to treat myself, but if I ever do I certainly intend to give trial to a much bolder scheme of dosages, beginning with not less than 25 millions. Initial dosages

of the various microbes and conduct of the case are as for septicæmia.

(3) **Adenitis and Lymphangitis.** (a) **Acute.**—The treatment of this differs in no way from that of a case of septicæmia.

(b) **Chronic.** — The only common form with which we have to deal is that due to the tubercle bacillus. The amount of research work done and the resultant literature upon the type of tubercle bacillus, human or bovine in origin, responsible for this condition can fairly be described as colossal. Some years ago I collected all the available records, and found that the one type had been isolated from tuberculous glands almost exactly as many times as the other ; but the younger the child, the greater is the likelihood of the type concerned being the bovine one. From the clinical observation that a case of cured glandular tuberculosis rarely contracts pulmonary tuberculosis in after-life, the curiously distorted view was offered and upheld by many that this was because the two types were antagonistic to each other. Elementary knowledge and common sense suggest that the reason is that the antibodies developed to one type are equally efficacious against the other type and persist for many years in the body. This matter has a very important practical bearing upon the choice of the appropriate tuberculin to use. Some there are who use human tuberculin in "bovine" infections and bovine tuberculin in "human" infections, while others there are who use bovine tuberculin for "bovine" infections and human tuberculin for infections by the "human" type. As one would naturally expect from the extremely close similarity of the antibodies produced by each "type," the results achieved by one school are practically identical with those produced by the opposition.

Consistency with the results of experience derived from the use of vaccines in all other cases of bacterial infection would induce us to feel that the nearer we can get in our tuberculin to the type of the infective agent the better, so to eliminate all chance of error I suggested years ago the employment of a polyvalent tuberculin, prepared from several strains of each type of bacillus, for all cases of tuberculosis. My view was endorsed by several well-known bacteriologists and pathologists, and has been widely followed. Thus in tuberculous adenitis we will assume that we are going to use a mixed polyvalent tuberculin in one of the forms advised on p. 172. Personally, I am here inclined to make use of the Bacillary Emulsion or of my own special tuberculin. In the former case the **initial dosage** may be .00001 c.c., in the latter .0001 c.c. Subsequent **dosages** and **intervals** should be controlled when possible by any reaction produced. Unfortunately the clinical condition varies so slowly in this disease that observation of the infected glands affords us little guidance; sometimes a slight swelling within twenty-four hours of a dose may be noticed, but more frequently it is absent.

We are therefore obliged to fall back on empiricism, and as a result of past experience and of experience in infections by other bacteria an interval of seven to ten days is usually employed. Tuberculous glands seldom seem to fail to benefit from a course of tuberculin, but inasmuch as the wise doctor will usually manage by hook or crook simultaneously with the use of vaccine to bring about some improvement in the conditions under which his patient lives, it is a practical impossibility to assess accurately the benefit which is actually derived from tuberculin. On the other hand, it is practic-

ally an impossibility for it to do any harm. The commonest sin committed in the vaccine treatment of adenitis is, as so often, a sin of omission, the failure to recognize the presence of and to deal accordingly with some secondary invader, usually a staphylococcus or a streptococcus. As a rule suppuration of the glands is due to invasion by these organisms, and it should be remembered that the latter necessarily must be antecedent to the former. If, therefore, a case of chronic adenitis is doing badly, a puncture of one or more of the glands and abstraction and culture of an almost microscopic portion is strongly indicated. By this procedure and the use of the autogenous vaccine, suppuration may well be forestalled. The initial dosage of such a vaccine for a child would be for the streptococcus 5-10 millions, for the staphylococcus 50-100 millions, according to age and weight.

(4) **Cerebro-spinal Meningitis.**—As already mentioned, cases of infection of the spinal and cerebral meninges are among the least suited to vaccine treatment, owing to the lack of communication between the blood and cerebro-spinal fluid and the consequent inability on the part of the antibodies carried in the former to reach the latter. Where most bacteria are concerned, so great is the handicap and so rapid the course run by the disease that vaccines are hardly worth even trying. In tuberculous meningitis, however, a chance may be given to tuberculin, and Buchanan and Raw between them report three successful cases.

In **meningococcal meningitis** a more extensive trial has been given to vaccine by Bourke, Abrahams, and Rowland (*Journal R.A.M.C.*, December 1915, p. 633). Out of a total of 160 cases under them, 81 were treated

with vaccine, 29 of these with living vaccine, 52 with a dead one. They tabulate their results as follows:

Treatment.	No. of cases.	Re- covered.	Died.	Still in Hospital.	Case mor- tality per cent.
Lumbar puncture only . . .	43	21	21	1	49
Combined with living vaccine	29	16	13	—	45
,, ,, dead vaccine .	52	24	28	—	54
,, ,, serum B and W	6	1	5	—	83
,, ,, Flexner	16	6	9	1	56
,, ,, Pasteur	11	4	7	—	64
,, ,, Mulford	3	—	2	1	67

The general high mortality rate they ascribe to the fact that their cases were received late in the disease. They conclude that no very distinct advantage could be ascribed to any special method of treatment, but they feel that attention should be drawn to the result in cases treated with living vaccine combined with repeated lumbar puncture. They gave the vaccine subcutaneously in dosages varying from 200 to 1,000 millions.

It should be pointed out that since their work was done, not only has the meningococcus been differentiated into many types, but also a much more efficient serum has been prepared at the Central C.S.F. Laboratories. However, if such an efficient serum be not available, trial may be given to an autogenous vaccine, and preferably to a living one.

(5) **Acute Rheumatic Fever.**—Keen controversy has raged around the question of the significance of the micro-organism known as the *Streptococcus rheumaticus* in the aetiology of acute rheumatic fever and its complications, such as endocarditis and chorea. Some laboratory workers, such as Harrison (*Journ. Royal Army Med. Corps*, January 1913, p. 1), who made unsuccessful blood cultures in twenty-six cases of acute

rheumatism, and claim that the blood of patients contains no specific antibodies to this microbe, deny that it has any connection with the disease; others, such as Fordyce, and Ruth Tunnicliffe (*Journ. of Infectious Diseases*, June 12th, 1909, p. 346), find that in acute rheumatism the opsonic index and other immune bodies run the definite course taken by these bodies for bacteria of indubitable aetiological significance to the diseases in which they are found. They accordingly consider that this streptococcus must play a part, if not the chief one, in the causation of these diseases.

Clinical experience with the vaccine would, in view of these divergent opinions, rightly be entitled to hold a prominent part in the discussion, but again it is not conclusive. Harrison (*loc. cit.*) found that a vaccine failed entirely to influence the course of the disease in six cases; but as any real guarantee is not forthcoming that the streptococcus employed in the preparation of the vaccine was really the streptococcus rheumaticus, his few experiments fail to carry much weight. Those of Buchanan (*Journ. of Vaccine Therapy*, vol. i. No. 1, p. 1) are much more valuable, inasmuch as the vaccine employed was compounded of two strains, one isolated by Beattie from the blood of a case of acute rheumatism and endocarditis, the other by myself, both from the blood "in vivo" from a similar case, and also post-mortem from the infected heart valves; this vaccine was accordingly beyond suspicion. Furthermore, Buchanan's cases were more numerous, being 14, 7 of which had chorea with or without endocarditis, and 9 of them acute pyrexial attacks with various complications. He concluded: "The results have proved most encouraging. I have come to the conclusion that the vaccine has a definite effect upon acute rheumatism, and this is best

seen when it is given early in the attack. In two cases it had definite results upon the endocarditis. In one it certainly prevented its onset where one would have expected it, for the attack was severe and accompanied by much arthritis. The arthritis rapidly disappears. There is no depressant effect. The fever subsides comfortably and easily. In more chronic cases it has a beneficial effect upon the joint lesions. In chorea it has a very beneficial effect, and in acute cases acts rapidly. It has a marked action in bringing down the pulse rate. It may prove useful in the subsequent history of acute cases to prevent relapse, and I would suggest that after an acute attack is over the vaccine should be administered at intervals for a considerable period to secure this effect. It acts best when given subcutaneously."

Buchanan used initial doses of 5-10 millions, increased subsequently to 10-25 millions under guidance of temperature chart and clinical conditions. The usual intervals were three to five days, occasionally seven days, and rarely daily inoculations were found necessary.

In view of Buchanan's experience and opinions, failure to give sufferers from this very far-reaching and life-wrecking malady the benefit of this vaccine seems rather to savour of negligence.

(6) **Malta Fever** (for prophylaxis see p. 81).—The earlier observations by Reid, Bassett Smith, and others upon the therapeutic use of vaccines in this disease are for various reasons not to be considered as reliable. Later observations by Kennedy (*Journal Royal Army Med. Corps*, September 1910, p. 317), Bassett Smith (*Journal of Hygiene*, December 1912), and others are much more dependable in the light of more recent knowledge, and the general opinion seems to be that

vaccines are sometimes of the greatest value. Bassett Smith, however, considers it to be contra-indicated when pyrexia is continuous or intermittent, but that with moderate hectic temperatures good results may be expected. For chronic cases it is the only method of value.

If, despite Bassett Smith's view—and other observers do not agree with his in this particular—vaccine be given to typhoid-like cases, the initial dose should not exceed 25 millions. In ordinary undulant cases 50 millions is suitable to begin with, and this dose may be increased at intervals of five to seven days, as indicated by temperature and clinical conditions, to 500, 1,000, or even 2,000 million organisms. Bassett Smith, in the type of case he considers suitable for the treatment, begins with 100 millions and increases gradually to 500 millions at intervals of five to seven days.

(7) **Plague** (for prophylaxis see p. 81).—In the treatment of pneumonic plague, vaccine has no place. As regards bubonic plague, the prospect is perhaps more hopeful. Rowland treated eighty-seven cases with a vaccine consisting, I believe, of a nucleo-proteid extract of the *B. pestis*: forty-three were septicæmic cases, and all died; forty-four were non-septicæmic, and all recovered. Unfortunately I am unable to give any details of his work.

(8) **Scarlet Fever** (for prophylaxis see p. 111).—Whatever be the correct rôle to be attributed to the *Streptococcus conglomeratus* or *scarlatinæ* in the causation of scarlet fever itself, it is beyond question that a streptococcus of the *conglomeratus* or some other type is nearly always responsible for such complications as endocarditis, myocarditis, and pericarditis, nephritis, and suppurative conditions of the glands, tonsils, and ears. [

I was the first to try the effect of the vaccine upon the course of the fever, employing a polyvalent vaccine of the organism isolated from the throats of twelve cases. In conjunction with Dr. E. W. Goodall of the Eastern Fever Hospital, I treated six cases of the uncomplicated fever with doses varying from 10 to 50 millions; we could not detect that it produced the least effect upon the course of the pyrexia. Boughton and Weaver (*Journal of Infectious Diseases*, 1908, p. 608) similarly tested vaccine in eighty-eight cases, and came to precisely the same opinion. This may almost be held to prove that the *Streptococcus conglomeratus* is not the real cause of scarlet fever, despite the vast experience of Gabritschewsky in its prophylactic use (see p. 111). His experience on the one hand, and mine and Boughton and Weaver's on the other, seem irreconcilable.

When, however, we come to the question of the utility of vaccine in the therapeutics of the complications, it is quite another matter. In no class of case are more consistently good results obtainable.

For my results in the case of a boy of eleven years seemingly at death's door with septicæmia, temperature of 104° F., and with low muttering delirium and free discharge of pus from both ears, see *Lancet*, September 11th, 1909, p. 780.

An initial dose of 10 millions autogenous *Staphylococcus aureus* and 12 millions of the polyvalent *Streptococcus conglomeratus* already referred to restored consciousness in twenty-four hours, and subsequent doses established convalescence in fifteen days. Boughton and Weaver (*loco cit.*) in thirty-one cases with complications which threatened to become chronic also secured prompt improvement in most instances.

Jochman and Michaelis (*Berliner Klin. Woch.*, May 16th, 1910) have also found the vaccine of considerable value, but prefer to combine it with antistreptococcic serum. This combination they regard as a sure preventive against nephritis.

If therefore we accept Gabritschewsky's results, and I know of no reason why we should not, the rôle of a vaccine of *Streptococcus conglomeratus* with regard to scarlet fever may be stated shortly as follows:

In prophylaxis of very great value. As a therapeutic agent in the course of the fever it is without any influence on the pyrexia, but possibly not without good effect in the prevention of complications.

As a therapeutic agent in the treatment of streptococcal complications it is of very great value, indeed of such great value that its use should on no account be withheld at the first signs of any complication due to this organism.

Initial dosages of 5-10 millions of an unsensitized vaccine, according to age and weight, may be used in cases of septicæmia, endocarditis, and nephritis, of 10-25 millions in suppuration of the glands, tonsils, ears, etc. If a sensitized vaccine be obtainable, double or quadruple these dosages may be given. Subsequent dosages and intervals will be controlled in the usual manner. A full course of treatment with high ultimate dosage, 250-500 millions, I consider to be advisable in most cases, in order to ensure no relapse or late complications. An autogenous vaccine is to be preferred, sensitized if possible, but inasmuch as mixed infection is the rule in suppurative conditions, a bacteriological examination of the pus must always be made with a view to the incorporation of vaccines of the associated organisms. For instance, the omission of the *Staphylococcus aureus*

vaccine from the mixture used in the septicæmic case referred to above would, I am convinced, have rendered nugatory the work which turned out so eminently successful.

(9) **Rabies** (for prophylaxis see p. 110).—In the treatment of rabies, once the disease has manifested itself, specific therapy is as yet of no avail.

CHAPTER X

DISEASES OF THE SKIN AND CONNECTIVE TISSUES

Disease.	Bacteria responsible or associated with.
Abscess	Staphylococcus, streptococcus, pneumococcus, <i>B. coli</i> , <i>B. typhosus</i> , <i>B. proteus</i> , <i>B. pyocyaneus</i> , <i>B. anthracis</i> , <i>B. Mallei</i> , <i>B. pestis</i> , <i>B. tuberculosis</i> , <i>Streptothrix actinomycosis</i> , etc.
Acne, comedones and seborrhœa	Acne <i>B.</i> , staphylococcus, streptococcus
Angina Ludwig's	Streptococcus
Boils and carbuncles	Staphylococcus
Cellulitis, mastitis, and whitlow	Staphylococcus and streptococcus
Eczema and psoriasis	Staphylococcus and streptococcus
Erysipelas	Streptococcus
Fistula	<i>B. tuberculosis</i> , <i>Treponema pallidum</i> , staphylococci, streptococci, <i>B. coli</i> , etc.
Gangrene (diabetic)	Staphylococcus
Glanders	<i>B. Mallei</i>
Impetigo and sycosis	Staphylococcus and streptococcus
Leprosy	<i>B. lepræ</i>
Lupus	<i>B. tuberculosis</i> (primary), staphylococcus, etc. (secondary).
Nile boil	Staphylococcus
Tropical ulcer or Oriental sore	<i>Leishmania tropica</i>
Sinuses and war wounds .	As for abscess, with addition of anaerobes various
Ulcers	<i>B. tuberculosis</i> , staphylococcus streptococcus, etc.
Veldt sore, Barcoo rot, septic sores of the tropics .	Streptococcus, staphylococcus, diphtheria bacilli
Whitlow	Streptococcus and staphylococcus

FROM this extensive list we see that the majority of the known pathogenic bacteria are associated directly or indirectly in the production of pathological conditions of the skin and subcutaneous tissue. Nor is this all. My oft-repeated warning of the frequency and importance of mixed infections holds with especial force in many of these cases ; to give two or three examples, the very numerous attempts to demonstrate a great utility for tuberculin in the treatment of lupus were foredoomed to failure from lack of recognition of the fact that in the majority of cases the lesion is secondarily infected by staphylococci or streptococci, and that a combined attack upon primary and secondary invaders is essential if success is to be secured. Again, my clinical failure to reproduce the wonderfully successful treatment of acne by means of a staphylococcal vaccine claimed by many was fully explained when the ætiological significance of the *B. acnes* was discovered, and the necessity again for a combined vaccine demonstrated. Finally, whatever be the initial causative agent of a condition of fistula in ano, whether *Treponema pallidum*, *B. tuberculosis*, or some other organism, secondary infection by the staphylococcus, streptococcus, *B. coli*, etc., is practically inevitable, and consequently a strong combined attack is indicated.

The fact that cure in these cases is sometimes brought about by the use of a single vaccine proves only that the resisting powers of the tissues were so good that even the imperfect help afforded enabled them to elaborate sufficient antibodies to overcome both sets of invaders, and in no way justifies the use of half measures only.

Before ever embarking on a course of therapeutic inoculations in diseases of the skin and subcutaneous

tissues, it is especially important that the doctor should assure himself that (1) a full and complete bacteriological examination has been made, and that the vaccine he proposes to use is really adequate in composition ; (2) he has taken a complete clinical survey generally of his case, so that he will not be tempted to rely on vaccine only and neglect to pay due attention, say, to the constipation and consequent absorption of toxins from the bowel so frequently present in cases of acne, or to the pancreatic insufficiency really responsible for a condition of diabetic boils or gangrene ; and (3) the additional antibodies he proposes to bring into being really have a chance of coming to grips with the enemy. All the antibodies in the world, for instance, might fail to make their way through the dense fibrinous walls of an old sinus or fistula, or through the dense coagula which may effectively prevent all circulation of the body fluids through the tissues in a case of Ludwig's angina. Scraping of the cavity walls in the first case, followed by the introduction of hypertonic hot fluids, and bold incisions in the second case, accompanied by full doses (60 grains t. d. s.) by the mouth of sodium citrate, will materially help to overcome these grave disabilities. To achieve success in vaccine treatment necessitates all the skill and thought and close clinical observation of any doctor.

While reference to the list will show that the bacteria concerned in the production of acute lesions of the cutaneous and subcutaneous tissues are very numerous indeed, two micro-organisms are responsible for by far the greatest proportion of all cases. These are the staphylococcus and streptococcus ; between them they must cause at least 95 per cent. of all cases of **abscess, angina, boils, carbuncles, cellulitis, mastitis, impetigo, sycosis**, and

whitlows, and I propose accordingly now to consider these all together.

It will be noticed that I have omitted from this list the various suppurative conditions of the skin and subcutaneous tissues common to warm climates, such as veldt sore, Barcoo rot, Nile boil, and Oriental sore, despite the fact that the first three are caused by staphylococci and streptococci. The return of our soldiers from abroad will probably soon render these conditions more familiar to doctors in England, and they present certain distinctive features which render their separate consideration desirable.

It will be assumed (1) that the surgeon has taken all necessary steps to release pus under pressure, to establish free drainage, to prevent the ingress of contaminating organisms from without, and to afford free access of all antibodies present in the general circulation ; (2) that the doctor has thoroughly investigated his case clinically, so that, for instance, the presence of diabetes has not escaped notice in a case of recurrent boils ; (3) that the bacteriologist has made a complete bacteriological examination, so that he has not failed to detect streptococci when greatly outnumbered by staphylococci or *B. coli* or to realize that the chief infective agent is of an anaerobic nature.

In the choice of appropriate schemes of dosages and intervals, several considerations enter, as for instance : (1) is the lesion a chance acute one ? (2) is it a chronic one ? (3) is it an acute manifestation of a chronic condition ? In the first case it may be deduced that as a rule the resisting powers of the tissues generally are adequate, but either a temporary fall therein has occurred, or there has been a temporary lowering of the local resisting powers prior to infection. In the second case it is

evident that a condition obtains of a generalized lack of resisting power in the tissues, due either to a congenital defect or deficiency of some constituent essential to the nutrition of the body and well-being of the tissues. A good example of this is probably afforded by acne, wherein the tissues generally seem to lack resisting power to the *Staphylococcus albus* and *B. acnes*, harmless organisms to the tissues possessed by the majority of individuals—a lack of resisting power, stated now by some to be either due to a lack of tin salts in the system or to be remediable by their administration. In the third instance the condition probably is due to a further local fall in the resisting power of tissues already generally lower than the normal. In the first case it may be assumed that with the restitution of the resisting power of the tissues, the lesion will disappear, and probably will not recur unless a renewed lowering occurs. In the second case it is hardly a question of the restitution of the resisting powers to their normal level, for the level normal to that individual is unduly low. Even if by means of a vaccine we succeed in bringing about the extinction of the infection, recurrence will result, unless the abnormal new high level be maintained by (a) prolonged vaccine treatment ; (b) subsequent prophylactic doses ; (c) general therapeutic measures directed to the improved metabolism of the patient. In the third case the local resisting power must first be raised as if we were dealing with case 1, and subsequently the resisting power of the tissues generally as if we were dealing with case 2, and this must similarly be maintained at its new high level.

Even our initial dosage will be influenced by these considerations; thus whereas as a rule high initial dosages are given in chronic cases, and low ones in acute,

the reverse rule may be applicable here. For instance, take the case of boils occurring (*a*) in an individual not subject to them ; (*b*) in an individual subject to them—and let us assume that a fresh focus of infection threatens to occur. In case (*a*) we know that the tissues generally are of good resisting power and capable of forming adequate antibodies ; in case (*b*) we know that they are not.

In (*a*) we know that the fall is temporary, and once removed, may not recur. We will therefore give a dose of 1,000–2,000 millions *Staphylococcus aureus*, and confidently anticipate that the boil will abort and have distinct hopes, at all events if we repeat that dose two or three times at weekly intervals, that no others will appear. To (*b*) we give only a dose of 250–500 millions, knowing that only a prolonged course of treatment, combined with other measures generally, is likely to be of permanent avail.

From what I have said it will be seen that it is no easy matter to lay down rules for initial and subsequent dosages and for intervals. If large initial dosages be used in acute cases with the idea of aborting the disease, as for instance dosages of 1,000 millions *staphylococcus*, 250 millions *streptococci*, *B. coli* or *pneumococcus*, subsequent dosages must be controlled by the clinical symptoms, and longer intervals (*i.e.* seven to ten days) than those usually employed in acute infections will probably be found appropriate under the same guidance.

If the lower initial dosages (*i.e.* $\frac{1}{4}$ – $\frac{1}{5}$ part of those given above) are employed, intervals of five to seven days will probably be indicated.

In cases where toxic symptoms are present, and the possibility of the infection becoming generalized has to be considered, as in acute cellulitis and Ludwig's angina,

general principles must be reverted to, and the initial dosage becomes for streptococcus 10-25 millions, staphylococcus 100-250 millions for an unsensitized vaccine, and double or quadruple these amounts for the sensitized vaccine, which is to be preferred.

Veldt Sore, Barcoo Rot and Septic Sores generally of the Tropics, excluding Nile Boil and Tropical Ulcer.—As already mentioned, the return of our troops from the warmer climates will almost certainly result in the doctor here being asked to treat many varieties of septic sores of the skin and connective tissues which previously he had never seen. As errors in diagnosis of the true infective agent may easily be made, and a drastic alteration of initial dosage may sometimes be necessary, especially in the case of Nile boils, it is well that he should be forewarned of these possibilities.

In the future, when called to treat any apparently simple inflammation of these parts, he will be well advised to ask the patient if he served in the army in Africa or Asia, and if so, to ascertain whether he suffered from a similar condition then. If this was the case, the doctor should be awake to the possibilities I have mentioned, and so avoid the assumption that he is necessarily treating a simple furunculosis or carbuncle.

Several pathologists of deservedly very high standing have come probably to erroneous conclusions as to the nature of the primary infective agent in these cases through failure to examine with sufficient care the lesions in their early stages. C. J. Martin and Bishop Harman found only staphylococci of low virulence in the pus even from the unbroken blisters which are the first symptom in the tropical septic sores.

Craig's examination of a large number of septic sores in the Sinai Peninsula in 1916 found true *B. diphtheriae*

in 25 per cent. of the cases, and noticed diphtheritic sequelæ to follow in a certain number of cases; in the others he found staphylococci. This high percentage of diphtheritic skin lesions was a chance occurrence, the *B. diphtheriae* being an accidental secondary infection, hardly likely to be repeated in such numbers. These sores were characterized by the presence of a tough, blackened, dry, very tenacious membrane covering the underlying ulcer. Warren Crowe (*Lancet*, November 16th, 1918, p. 667) examined ninety-eight non-membranous sores in as many persons; he found that the younger the blister examined, or the greater the care exercised in cleaning up an open septic sore before taking cultures, the higher was the percentage of cases in which streptococci were found and the lower the percentage in which staphylococci were found. His figures were as follows. Of the 98 sores, 33 were sterile, 65 showed the presence of microbes. Of these 65 cases:

Streptococci were found	in 59 cases = 90.8%
Streptococci in pure culture	„ 39 „ = 60.0%
„ with staphylococci	„ 17 „ = 26.1%
„ „ diphtheroids	„ 3 „ = 4.6%
Staphylococci in pure culture	„ 4 „ = 6.2%

Had he failed to clean the ulcerated surfaces thoroughly or waited till the blisters became quite purulent, he would probably have found staphylococci in all, like Martin and Bishop Harman.

Vaccines of staphylococci he found without any apparent effect at all upon the lesions, whereas small doses of streptococcal vaccine, either autogenous or stock from similar cases, produced very marked focal reactions with an outpouring of serum. Large doses were liable to produce a fresh outbreak. Crowe therefore regards

streptococci as the primary infective agent, and the staphylococci, *B. diphtheriae*, and diphtheroid bacilli as secondary invaders. Whether this view is correct or not, his work clearly shows the necessity for avoiding hasty generalizations and the assumption that a staphylococcus is sure to be the infective agent.

In view of his findings, Crowe advises the use of mixed polyvalent vaccines of both streptococci and staphylococci, these being made by growing primary cultures of either microbe for twenty-four hours in peptone broth of acidity + 6, to which glucose 1 per cent. and human serum 2-5 per cent. is added; the growth is sterilized by the addition of antiseptic, and not heated. He found that very small initial dosages gave good results, and that with quite moderately large ones there was a danger of producing a fresh crop. He therefore advises, as the initial dosage, half a million only of each microbe; this is repeated twice weekly until all lesions are cured, no fresh ones appear, and no old scars are caused to weep afresh after inoculation. As these small doses have no influence in preventing relapse, he then raises the doses to 1, 2, 4 millions bi-weekly, then to 8, 16, 32 millions weekly, each dose being repeated once or twice. By these means the average stay in hospital for over 600 cases was reduced to ten days, from a prior duration of about one month; *i.e.* an average of four doses sufficed for cure, prophylaxis being continued after discharge from hospital.

Nile Boil.—This condition was very fully studied at Khartoum by Capt. R. G. Archibald. It begins, very like the sores just mentioned, with a tiny blister, which soon becomes surrounded with a bright red areola varying in size from that of a sixpenny piece to that of a crown. If even twenty-four hours after the first sign

of trouble the head of the blister be lifted off, a small slough will be seen, which soon extends in area. General hardening and swelling of the surrounding tissues rapidly ensues, and they become a dusky purple. A hard brawny lump is formed with the central slough steadily increasing in size, pus forms, the slough is cast off, and a deep-seated ulcer is formed with considerable destruction of tissue. Healing occurs from the bottom, and a deeply pitted purplish scar always results, unlike the case of the septic sores, where no scar is formed. The condition is an excessively tender and painful one from the beginning. I have described it fully, so that it may not be confused with a carbuncle, from which it is differentiated by its initial slough and complete absence of pus until near the last stage. Archibald (*Journal of Vaccine Therapy*, vol. i. 1912, p. 314) states that the lesion is due to the staphylococcus, which is usually an aureus, occasionally an albus, rarely a citreus, and claims to have obtained excellent results by following an initial dose of 250 millions of vaccine, sterilized by heating to 58° C. for forty minutes, and the subsequent addition of 0·2 per cent. lysol, with a dose of 500 millions four days later, and then giving 500 millions weekly, until six doses in all have been given. In young children he employs dosages of 2 millions upwards. He states that, as a rule, cure is effected with three or four doses, but he advises the full course of six doses to secure better immunity. Nile boils are very prevalent towards the end of the summer months, are intensely painful, and have a very serious effect on the patient's general health and peace of mind. Archibald concludes his article by stating that "under this line of treatment an assurance can be given of a certain and successful cure." I relied on this statement, and gave

this assurance to the first case of Nile boil I ever saw, a case sent me by Capt. Archibald himself. The lady was almost due to return to Egypt, and I was only able to give her two injections. These both caused intense focal swelling and pain, and I could notice no immediate improvement. She continued treatment on board ship, and wrote from Cairo to say she was still bad. The vaccine I used was one of *Staphylococcus aureus* 2 parts unsensitized to 1 part sensitized. The recent paper by Crowe (*loco cit.*) now makes me wonder whether Archibald is right with regard to the bacteriology and vaccine treatment. Crowe, after examining thirty cases, concludes that the *Staphylococcus aureus* is *not* the cause of Nile boils, though it may possibly be responsible for the late pus formation. He regards a *staphylococcus* which is white on agar but yellowish on serum, and probably allied to the *Staphylococcus epidermidis albus*, as the causative agent, and states that if the superficial tissues be carefully sterilized, the head of the boil lifted off and serum obtained by dry-cupping, cultures made in the glucose serum peptone broth already referred to will yield pure growth in the majority of cases ; a growth characterized by formation of coarse granules and absence of turbidity. This growth may be sterilized by the addition of 0.5 per cent. lysol and used as vaccine. He finds it extremely toxic, to such a degree indeed that only half a million is the appropriate initial dose ; subsequent doses are given as laid down for septic sores on p. 198. If this procedure be adopted, the slough being thoroughly divided by crucial incisions at the same time as the first dose is given, instead of awaiting pus formation as is the usual practice, cure may be expected in forty-eight hours. Larger doses than 32 millions he found needless

in prophylaxis, and only causative of considerable swelling and stiffness at the site of inoculation.

As I know Crowe to be a very painstaking worker and no fanatical advocate of absurdly small doses, and my own very limited experience in three cases with large dosages has not been very happy, I am inclined to give his views the preference over those of Archibald, despite the great experience of the latter. However, it is an easy matter for the doctor who chances to have a case, first to give trial to Crowe's recommendations, and if these fail, to fall back on Archibald's.

Tropical Ulcer or Oriental Sore.—This condition is due to the micro-organism known as "Leishmania tropica."

Rowe (*B.M.J.*, March 9th, 1912, p. 540) has prepared a vaccine of the parasites by growing them in Nicolle Novy McNeal medium for seven days and sterilizing by the addition of glycerine. He uses initial dosages of 0.125 c.c. of this vaccine, and claims to secure complete and permanent cure in two to three weeks.

Acne, Comedo, and Seborrhœa.—In these conditions the primary infective agent almost certainly is invariably the acne bacillus. If pustulation supervene, the staphylococcus, usually the albus, but occasionally the citreus or aureus, has become a secondary invader. I have seen one case of pustular acne of exceptional severity, and one case only, in which the staphylococcus seemed to play no part whatever. A twofold difficulty exists in these cases: not only does there exist some general constitutional defect—now said to be remediable by the administration of tin salts—but unless pustulation occurs, the bacteria also are practically outside the reach and influence of the various antibodies.

Before beginning vaccine treatment, it is therefore necessary to prevent, as far as possible, all absorption

of toxins from the bowel, etc., to promote elimination, improve the general condition of the body, and pay close attention to the local conditions, using hot or Turkish baths, friction, massage, ethereal or other suitable soap solutions, and such medicaments as may help to promote removal of the sebum, limit its formation, and cause the closure of the distended glands and ducts.

Many dermatologists deny to vaccines any place in the treatment of these conditions, but all I can say to this is that by means of vaccines and such measures as I have indicated I have cured, and cured permanently, many cases which had had prolonged treatment at the hands of dermatologists to whom it would be rank heresy to deny a high place in the esteem of their fellow-specialists. I may perhaps be accused of being spiteful, but I have no desire to be so, when I retort that I know of no dermatologist in this country whom I consider a sufficiently good clinical bacteriologist to be qualified to administer a course of vaccine treatment. Acne is one of the most difficult diseases to treat with vaccines, requiring as it does careful repeated bacteriological examinations to assist in our scheme of dosages and intervals.

Clinical changes occur so slowly that they give very little help, and the change in the condition seen to-day is very often the result of doses given weeks ago; in the meanwhile, changes of dosages which ought never to have been made may have been made, and made in the absence of bacteriological examinations.

Furthermore, many have a horror of exciting those appropriate focal reactions which here are almost the only index of adequate immunizing response. While it must be admitted that great harm may be done by exciting undue focal disturbances, the reactions must

be adequate and be evinced within twelve to forty-eight hours of the administration, *i.e.* at such a time as the dermatologist is unlikely to appoint for a fresh interview with the patient. I know of no bacterium other than the acne bacillus to which patients show such an extraordinary variation in their power of response. To some, higher dosages than 10-25 millions can never be given with safety; others make no response at all till they are given 100-250 millions. A simultaneous variability towards the associated staphylococcus I have never yet seen. As I wrote years ago, acne and asthma are perhaps the most difficult diseases in which to employ vaccines, yet at the same time they sometimes show really brilliant results.

There are beyond doubt at least two varieties of the acne bacillus, and no stock acne bacillus vaccine should be used unless it can be depended upon to contain both of these.

A stock staphylococcus vaccine is usually reliable, but not always so; hence it will be understood that the double autogenous vaccine is to be preferred, although stock ones, with the proviso I have made, will be found suitable in the majority of cases.

The appropriate initial dosage of the staphylococcus may be set down for all cases at 250 millions. That of the acne bacillus, in view of the marked susceptibility sometimes existing, is harder to fix. In this disease I believe it better to make a diversion from the more usual custom, and begin with a vaccine of the acne bacillus alone, in order if possible to determine clinically the appropriate initial dosage. Begin therefore with 5 millions, inspect the case carefully next day; if no reaction is seen by doctor or patient, repeat in three to four days; if still no response, give 10 millions in three

to four days, and so on, until the dosage is found which just gives a definite focal reaction. Then wait a week, and reinoculate with half that dose combined with 250 millions staphylococcus. I am satisfied that by this procedure very much better results can be achieved than by any other. Treatment in bad cases may have to be prolonged for six or even twelve months, and dosages ten to twelve times the initial "reaction" dosages may be advisable in order to prevent relapse.

Acne Rosacea.—Lane (*B.M.J.*, November 8th, 1918, p. 515) records a case of this disease to which he empirically gave a dose of 250 millions mixed staphylococcus vaccine. This immediately brought on a reaction with marked accentuations of the local lesion. Five doses of 500 millions were given at weekly intervals, during which the patient made marked progress. Six doses of 1,000 millions and two of 2,000 millions completed the cure. Six months later there was no sign of a recurrence.

Eczema and Psoriasis.—While I do not consider, *pace* some other bacteriologists, that local bacteria are ever the prime cause of these conditions, there is no doubt that bacteria are often a factor in producing some of the symptoms and in maintaining and aggravating the condition. It may therefore be deduced that a vaccine will probably fail to cure the condition, but may produce considerable amelioration and enable procedures previously ineffectual to bring about the cure. The two bacteria commonly associated with the lesions are staphylococci and streptococci, occasionally *B. xerosis* and other diphtheroids and coliform bacilli are also found.

My results have been in conformity with my expectations, and in one case of eczema and one case of psoriasis considerably beyond them. The latter case was really

a test case, because the patient had had the disease for about thirty years, had been in that time under the care of at least six of the world's most famous dermatologists, including Unna, had had the means and the will to take any steps necessary for cure, yet remained in such a condition that for months every year he lived in a suite at an hotel in order to avoid appearing in public. After about nine months' treatment with a mixed vaccine of staphylococcus and a diphtheroid we dined together in public, and during the last five years he has had only two or three slight recurrences, at once checked by vaccine and a few tar baths, which always suited him best. In this case I began with 250 millions staphylococcus and 50 millions of the diphtheroid, ultimately reaching 2,000 millions of the former and 500 millions of the latter.

In eczema the initial dose of streptococci is 50 millions, of staphylococci 250 millions, and the ultimate dosages necessary may be 500-1,000 millions of the former and 2,000-10,000 millions of the latter. A long course of treatment is usually necessary, but in a very few cases marked improvement has occurred after five or six of the quite small dosages.

Other workers such as Miller, Shivdas, Crofton, McDonald, and Whitfield claim very good results indeed with just such dosages as the above.

Erysipelas.—That a member of the *Streptococcus longus* group, to which the distinctive term "erysipelatis" has been applied, is the true and sole causative organism in erysipelas may be taken as being satisfactorily demonstrated, as this bacterium can be invariably isolated from the scarification exudate obtained from just outside the growing margin, and the curves of the various antibodies found in the blood during the

course of the attack follow precisely those lines which theoretically they ought to do in the case of a disease and its causative organism.

The chief symptoms in this disease are due to the endotoxins of the streptococcus circulating through the tissues, and theoretically these can best be combated by the administration of a serum containing the appropriate anti-endotoxins. Clinical experience and theory in this case support each other, and for the relief of the more important symptoms an antistreptococcal serum true to type should be freely given. In the administration of the various antisera one most important fact is constantly overlooked, and to this and not to inherent defects in the serum are many of the failures in serum therapy probably attributable. It is as follows: If the serum be given in inadequate amounts a proportion, greater or less, of the toxins, etc., circulating through the tissues fails to be combined with their respective antibodies; if, on the other hand, a certain excess of serum be given, these combinations may be completely inhibited, for a time at least. So that we see a deficiency of antiserum or an excess of it may equally fail materially to benefit the patient; whereas if the correct amount be given, more or less complete neutralization of the toxins, etc., may be effected, and the patient will benefit accordingly.

Antistreptococcal sera are, however, as a rule, deficient in bactericidin and lysin, the antibodies which lead to the death and solution of the infecting microbes, so that their influence is not great in bringing about the extinction of the infection.

This theoretically can best be assisted by the use of vaccine sensitized or unsensitized; the important point is whether clinical experience and theory here

correspond. Laboratory experiments show that the administration of a vaccine does lead to the production of the essential antibodies, and some clinical observers find in their observations proof of its clinical value, both in influencing favourably the course of the attack and in diminishing greatly the liability to extension and relapse. Other observers fail to find any direct benefit resulting from the use of vaccine.

Ross and Johnson (*Journal Amer. Med. Assoc.*, 1910, p. 966) have made the most extensive study of any observers of the clinical value of vaccine treatment in erysipelas, having treated therewith all the cases—fifty in number—admitted to Toronto General Hospital in 1908. To their comparison of their results obtained in 1909 by more specific measures in nineteen cases with those obtained in 1908 in a series of nineteen cases treated with vaccine, not too much weight should be attached, and this the authors point out themselves; for the severity of erysipelas markedly varies, not only with different individuals, but also from year to year, so that it is hardly fair to compare the results of one year with those of another. What is really of more value is the impression left on their minds by their experience of the fifty cases; for, rightly or wrongly, I have always held the view that while figures may be twisted to prove anything, the impressions of honest skilled clinicians are free at all events from this defect.

Ross and Johnson found the most striking effects lay in the rapid subsidence of toxæmic symptoms, such as mental unrest, delirium, and profound malaise; even the very severe cases almost invariably felt different within twenty-four to thirty-six hours of the first inoculation. Locally, as a rule, some further extension of the process occurred, until after a second inoculation

on the following day, or even until after a third ; but whatever extension did occur, it was remarkable in that (1) the colour was brownish red instead of an angry red ; (2) the swelling of the skin was less ; (3) the tenderness over the area of extension was less acute or abolished ; (4) pain was diminished ; (5) the growing margin was rarely raised, but faded off into the adjacent tissues.

They found that the pyrexia subsided more rapidly and long-continued pyrexia was not encountered, and that complications and sequelæ seemed to occur much less frequently.

Initial dosage in severe cases was 10 millions, in less severe 20 millions.

On the second day the severe cases received another 10 millions if improvement was evidenced by clearing of the intellect and a less intense degree of inflammation ; if no improvement was evidenced, a second dose of only 5 millions was given the following day. Here I think their procedure was wrong, and that in such cases the dosage should have been repeated or even increased to 20 millions, instead of being diminished. In the less severe cases immediate improvement was almost always shown, and 10 millions were given as the second dose. Five, 10, or 20 millions were then given every other day until a week had elapsed from the establishment of a normal temperature and the disappearance of all erythema. Other observers have recorded small series of successful cases.

In view of more recent advances in bacteriology generally and in vaccine treatment especially since Ross and Johnson's work, I would suggest that the best way to utilize specific therapy in erysipelas is as follows : In all cases showing any degree of toxæmia first give an adequate but not excessive dose of a reliable

serum, "Antistreptococcus erysipelatis"; this dose may be about 50 c.c., but will vary with the severity of the symptoms and with the make of serum, and should be indicated by the makers for a man of average size. This serum should be repeated or not, according to clinical symptoms. As soon as the toxic symptoms are under control, begin with vaccine treatment in order to bring about the death of the streptococci and so prevent extensions or relapse. The vaccine is best "autogenous," but in default a reliable stock vaccine of this type of the organism should be used. If the vaccine be unsensitized, the initial dose may be 10 millions; if sensitized, 25-50 millions, according to the severity of the attack.

If no antistreptococcus serum be obtainable, then one must fall back on a sensitized vaccine with an initial dose of 25 millions, and only in its default upon an unsensitized vaccine with an initial dose of 5 millions. Subsequent dosages and the intervals will be determined as usual by the reactions produced, both focal and constitutional, bearing in mind that the best possible sign of a reaction having occurred will be disappearance of toxic symptoms, fall of temperature, and general clinical improvement, signs of retrogression or failure to make any improvement being a signal for reinoculation. So long as the patient steadily improves, do not, without good cause, increase the dosage until convalescence sets in. It should then be steadily increased until a maximum dosage of 500-1,000 millions unsensitized or 2,000-5,000 millions sensitized bacilli has been attained, with a view to the removal of all chance of relapse or recurrence.

Fistula, Sinuses, War Wounds, and Ulcers.—In the vaccine treatment of these conditions four main diffi-

culties are encountered, viz.: (1) In establishing a correct and complete diagnosis of the infecting agents. Infections are nearly always mixed, and sometimes very mixed indeed. Take, for instance, "fistula in ano" in the case of a woman. The primary agent may be the *B. tuberculosis* or *Treponema pallidum*. Upon this a gonococcal infection may become superimposed, subsequently to be further complicated by streptococci, staphylococci, *B. coli*, *B. pyocyanus*, etc., singly or in conjunction. It would be no rarity for such a case to be treated with a vaccine of *B. coli* only, and when the inevitable failure ensued for vaccine treatment to be well damned. War wounds, again, usually present a very complex bacteriology, anaerobes or aerobes of various sorts occurring either in association or in succession. (2) A second difficulty is presented by the fact that vaccines of these various microbes cannot always be prepared or safely employed. This holds with regard to the *Treponema pallidum* and almost all, if not actually all, of the anaerobic microbes. (3) The condition is very frequently a chronic one; pathological changes have occurred in and around the lesions which prevent the free access of the various antibodies, or such things as sequestra and foreign bodies may be present which cannot always be adequately dealt with by the surgeon. (4) Too rapid healing may occur in the superficial structures, leading to retention of pus, etc., in the deeper parts, and consequent complications. However, forewarned is forearmed, and difficulties exist only to be overcome, and this can usually be done if the possibility of the existence of these difficulties be thoroughly grasped.

Perusal of the list on p. 190 will show that almost any one of the pathogenic bacteria may be concerned

in these conditions. As regards the anaerobes, very little is known concerning their treatment by means of vaccines. Vaccines have been used in the case of a few, as, for instance, of *B. Welchii*, *Spirochæta Vincentii*, *B. fusiformis*, and a few spirilla. The objection to their use is twofold: (a) the difficulty in preventing the presence of spores and at the same time making an effective vaccine; (b) the great toxicity as a rule present in them. Fortunately the natural tendency is for the anaerobes to die out and be replaced by acid-forming aerobes. In the combat of these latter, vaccines certainly find a definite sphere of usefulness.

The initial dosages will be decided partly by the clinical condition both of the patient and the lesions, partly by the consideration that healing must be necessarily slow, and must above all take place from the bottom outwards. Several times when I was in charge of the surgical section at the New Zealand Convalescent Hospital my greatest difficulty when using vaccines was to retard healing in the superficial parts, because I knew I was often dealing with deep tortuous sinuses, at the bottom of which lay a sequestrum, or possibly a foreign body such as a piece of cloth or splinter of metal, which perhaps it was advisable to leave to come away naturally. The presence of these foreign bodies is clearly indicated whenever a small dose of vaccine leads to pain or swelling in the region of the wound, an accumulation of pus small or large in the deeper parts of the tissues, followed in a few days by its discharge along the old tract and the consequent breaking down of the healed superficial tissues. The onset of a rigor twelve to twenty-four hours after the administration of the vaccine is *in these cases* an infallible index of the presence of a sequestrum or foreign body at the bottom of a closed sinus. In cases such as

these the dosages are kept lower than one would otherwise employ. For instance, 100 millions staphylococci takes the place of 250 millions, 10 to 25 millions streptococci, *B. coli*, or *B. pyocyanus* the place of 50 millions, and so on.

Of course if drainage can be well maintained, if the lesions be superficial, and the chief obstacle to healing be apparently lack of general vitality and reactive power of the tissues locally, a bolder dosage is indicated. The control of dosages and intervals will mainly lie in the clinical progress of the parts concerned and of the patient generally.

The judgment of all those who have had any considerable experience of the use of vaccines in these conditions is that indubitably vaccines are of very great value indeed in speeding up the healing processes, and especially is this so in just those cases where help is most needed—viz. when the patient is becoming cachectic, and when the wound has become sluggish and indolent, as if the tissues generally were lacking badly in the power to make any immunizing response without assistance.

In two classes of case they have an especial value: (1) in those where sequestra are continually coming away, for in these vaccines considerably speed up their separation and greatly assist in the limitation of the destructive processes; (2) in those especially liable to secondary haemorrhage and to recurrent pyrexias. Goadby (*Lancet*, 1916, vol. ii. p. 89), working on cases of Jocelyn Swan's at the Royal Herbert Hospital, shows from an analysis of 101 cases how potent is the effect of proper vaccine treatment in diminishing the liability both to secondary haemorrhages and post-operative rises of temperature.

It is painful to contemplate the number of men inevitably destined to spend their lives with discharging sinuses and chronic ulcers, unless specific treatment is accorded them along with continued proper surgical supervision and treatment, and it is the duty of all doctors to afford each and all of these sufferers from such distressing disabilities the benefits almost certain to be derivable from a patient, long-continued, and properly controlled course of vaccine treatment. Shera, in his little book *Vaccines and Sera*, p. 80, gives short abstracts of twenty-five such cases, which show well the powerful determining action towards eventual and complete cure possessed by the appropriate vaccines, which obviously are best autogenous in nature.

In cases necessitating repeated operation, the advisability may be mentioned of administering, two to three days before operation, a prophylactic dose of some such vaccine as the following :

B. coli	100	} millions
Staphylococcus	:	:	:	:	:	:	500	
Streptococcus	:	:	:	:	:	:	100	

with a view to diminishing the risks of hæmorrhage and pyrexia.

Glanders.—The rarity of this disease being equalled only by the gravity of the prognosis, the latter consideration entitles it to mention in this little book, especially as in vaccine appears to rest the only hope.

I can find only six recorded cases, in three of which complete cure appears to have resulted. The vaccine is powerfully toxic, and produces at the site of inoculation and possibly around the lesions the well-known mallein reaction, which proved so painful in two of the cases that treatment had to be abandoned. This difficulty

would possibly, nay probably, be obviated by the use of a sensitized vaccine.

The three successful cases are recorded by Wright (*Studies in Immunization*, pp. 406-9), Zieler (*Wien Med. Klin.*, May 2nd, 1909), and Billings (*New York State Journ. of Med.*, May 1910). Zieler's case was an especially bad one, yet within three months cure was effected. Wright's case took about the same time.

Owing to the causes already mentioned, dosages have to be kept very low. Wright began with a dose of 2 millions, and the highest he attained was 5 millions. Dosages and intervals are to be controlled as usual by the reactions and the clinical signs and symptoms.

Leprosy.—All workers upon this disease are satisfied that in the *B. lepræ* exists the true causative agent of the disease, but hardly two are agreed upon the point as to whether this organism has yet been isolated in artificial cultures, and if so as to what are its characteristics. At the International Congress of Medicine held in London, the number of cultures shown as being probably the true *B. lepræ* was almost bewildering. Perhaps the bacillus isolated and described by Kedrowski has the most supporters. By far the major portion of vaccine work in leprosy has been done by Rost, who employs a vaccine prepared in a very peculiar manner from a strain closely resembling Williams's chromogenic streptothrix. Speaking from memory, I think Rost considers this probably identical with Kedrowski's bacillus. His earlier work is recorded in the *Indian Medical Gazette*, July 1911 and July 1912, and details are given of numerous successful results brought about with doses of 1 to 3 c.c. of his vaccine. He recently claims to have effected further improvements in his vaccine, and to be securing even better results than before.

Crofton (*Therapeutic Immunization*) states that he has obtained focal and general reactions in ten cases with a vaccine he prepared, but that his results so far are not good enough to warrant description.

Lupus.—This disease is notable chiefly for the acrimony imported into the discussion regarding the value of tuberculin treatment. When the warring factions were almost exhausted, it was demonstrated that secondary infection by staphylococci and streptococci played a very important part in a considerable percentage of the cases, and that tuberculin could not be expected to cure these unless and until due regard had been paid to these pyogenic organisms. Meanwhile, other remedies, such as radium, carbonic snow, ultraviolet light, especially that derived from the open Wolfram light, were much championed, with the result that vaccines and tuberculin have been relegated to the background.

Whatever be the real merits of specific treatment, there is no doubt that the necessary course must be a very prolonged one, making great calls on the purse of the patient and the patience and skill of the vaccine administrator. The liability to relapse is also a frequent source of disappointment to the advocates of any special form of treatment.

I have had very little experience of the specific treatment of this disease with vaccines and tuberculin, but have seen many very successful cases treated with the Wolfram arc light, so always prefer to advise that this latter treatment be given a trial. If it be decided to give vaccine treatment a trial, I can only again impress the urgent necessity, not only of searching out thoroughly any secondary infection at the beginning of treatment, but also of maintaining a close watch throughout the

course, lest, unknown to the administrator, a staphylococcus be supplanted by a streptococcus, or vice versa. The appropriate initial dosages of any of these organisms will be the same as in eczema (see p. 204). As regards the choice of tuberculin, see pp. 172-180.

CHAPTER XI

DISEASES OF BONES AND JOINTS

Disease.	Bacteria causative thereof or associated with.
1. Acute osteitis, periostitis, and osteomyelitis .	Staphylococcus, streptococcus, pneumococcus, <i>B. typhosus</i> , <i>B. coli</i>
2. Chronic osteitis, periostitis, and osteomyelitis	As for (1) with addition of <i>B. tuberculosis</i> , <i>Treponema pallidum</i> , <i>B. pyocyaneus</i> , <i>M. tetragenus</i> , etc.
3. Acute arthritis .	<i>Streptococcus</i> , <i>gonococcus</i> , <i>pneumococcus</i> , <i>staphylococcus</i> , and <i>pyogenic bacteria</i> generally
4. Chronic arthritis .	<i>B. tuberculosis</i> , <i>Treponema pallidum</i> , <i>gonococcus</i> , <i>streptococcus</i>
5. Rheumatoid arthritis .	Associated therewith all bacteria causing pathological conditions of the digestive tract, especially <i>Streptococcus salivarius</i> and <i>fæcalis</i> , <i>staphylococcus</i> , <i>pneumococcus</i> , <i>B. coli</i> , and <i>anaerobes</i> of various sorts, such as <i>B. Welchii</i> , <i>spirilla</i> , <i>spirochætes</i> , and <i>B. fusiformis</i>

. (1) and (3) **Acute Osteitis, Periostitis, Osteomyelitis, and Arthritis.**—Acute pathological conditions of the bones and joints are usually set up by some injury, grave or so slight as almost to fail to attract notice, and the subsequent access of bacteria, either introduced directly through a breach of surface or carried thither by the circulating fluids of the body, in which case it is obviously necessary that the primary source of infection should

be discovered and receive adequate attention. For instance, an acute infection of the knee joint may be set up by streptococci, carried into the joint on a piece of clothing driven in by a bullet or piece of shrapnel, or a slight knock on the knee may lead to immigration of pneumococci from a chronic focus such as I have described as existing in many lungs, of gonococci from an infected urethra, or of the *B. typhosus* from the bowel or kidney in the case of a carrier of this microbe. It will thus be evident why the most skilled surgical measures directed against the acute local manifestation may not suffice to ensure speedy recovery, unless adequate steps be taken to eradicate the bacteria from the primary focus of trouble.

In this direction vaccines may be of very material help, and the benefit accruing to the primary focus therefrom is not limited to this focus, but is also extended in the direction of the acute manifestation.

If the bacteria be introduced from without through some breach of surface, mixed infection is likely to occur, and the possible presence of anaerobic bacteria should not be overlooked ; whereas if the bacteria have simply migrated from some focus within the body, simple infection by one variety of microbe is the rule, even if the bacteriology of the primary focus be a complex one. Only very occasionally does a double infection seem to occur ; nevertheless the possibility of its existence should not be overlooked, and careful bacteriological examination of direct smears as well as by cultural methods should be made of the matières morbi obtained either at operation or by puncture of the joint. If delay is permissible, much is to be said in favour of aspiration of the pathological fluid prior to operation, as thereby opportunity is given for the preparation of a

vaccine—better a sensitized one—wherewith the patient may be prophylactically treated. In this way the very real danger of such complications as extension or septicæmia and secondary haemorrhage may be materially reduced. The paper by Goadby referred to in the last chapter and some of Shera's cases show the extreme value of this procedure in the treatment of severe war wounds of the joints, and the dosages given on p. 211 for wounds of the connective tissues are equally suitable in these cases.

The great assistance that vaccine treatment can afford the surgeon in serious infective conditions of the bones and joints is well illustrated by a case recorded by me (*Lancet*, September 11th, 1909, p. 780) of very extensive infection of the knee and ankle joints, muscles and veins of the leg by the pneumococcus. Despite the presence of septicæmia and the very bad general condition of the patient, a single dose of 50 millions of the autogenous pneumococcal vaccine sufficed to turn the scale, and recovery was practically complete within two months.

Infections by the pneumococcus, streptococcus, and gonococcus appear to do equally well, but it must be mentioned that in the case of the gonococcus relapse is especially liable to occur unless the focus in the urethra is completely exterminated. It is no easy matter to determine whether and when this has been achieved ; so that in order to eliminate risk as far as possible, a prolonged course of treatment and high ultimate dosages are strongly to be recommended. I have sometimes continued treatment for several months after the apparent completion of cure, and used final dosages of 2,000–5,000 millions gonococci ; in cases so treated I have never yet seen relapse.

I may briefly refer here to the great help sometimes afforded by vaccines in the determination of the infective agent in cases of acute arthritis, especially when these are of a recurrent nature. Puncture of the joint being contra-indicated or cultures proving sterile, the patient is put to bed, and his pulse and temperature taken every three hours. A **diagnostic** dose of a vaccine of the organism suspected as being in causal relationship to the condition is then given, the pulse and temperature recorded as before, and careful watch kept on the clinical condition generally and of the affected joint in particular. With a suitable diagnostic dose, viz. 250 millions streptococci or pneumococci and 250-500 millions gonococci or *B. coli*, a perfectly unmistakable focal and general reaction should be secured if the vaccine and infecting organism correspond. If they do not correspond absolutely, nothing should happen, and twenty-four hours later trial may be made of another vaccine. I have never seen the least ill-effect produced in a patient, despite on several occasions a general reaction of considerable severity, and sometimes the information so obtained has been of the utmost value.

The initial dosages of the various organisms are the same as in acute infections of the subcutaneous tissues (p. 193); if, however, the general condition be very bad, they may be reduced to correspond with those given in cases of septicæmia (p. 178).

Subsequent dosages and intervals will be controlled in the usual way by reactions focal and general, by the pulse and temperature chart, and general clinical signs and symptoms. As already mentioned, it is wise to continue treatment for some time after recovery appears to have been completed.

For vaccines in acute arthritis due to the strep-

tococcus rheumaticus see Acute Rheumatic Fever (p. 183).

(2) **Chronic Osteitis, Periostitis, and Osteomyelitis.**—Nearly all I have said with regard to the acute forms of these diseases holds with regard to the chronic forms. There is the same need for accuracy in the bacteriological diagnosis, the same or even greater value in the diagnostic use of vaccines of the supposed offenders, the same necessity for acting in conjunction with the surgeon, the same value in vaccines as curative agents and as agents for the prevention of extensions, relapses, secondary haemorrhages; and post-operative pyrexias. An additional warning has, however, to be given, and that is with regard to the frequency with which the *Treponema pallidum* especially, but also the *B. tuberculosis* are concerned in chronic diseases of bone. The facilities now afforded for the making of the Wassermann test and the increased reliance which can now be placed upon this test render unpardonable a failure to recognize a syphilitic origin, and help by the process of exclusion in arriving at a correct diagnosis of tuberculous origin. It may also be mentioned that recent work with regard to the question of variety of tubercle bacillus concerned in chronic tuberculosis of bones and joints seems to show clearly: (1) that in cases below the age of three years the bovine bacillus is responsible for 80 per cent. of the cases, but that as the age of onset increases, the frequency of occurrence of this variety very rapidly diminishes, so that at five years of age and thereafter the human type occurs as frequently as the bovine type; (2) that a family history of tuberculosis or a history of prolonged contact with a case of pulmonary tuberculosis points very strongly in favour of the infecting agent being of the human type. In the minds of some

this matter is of considerable moment with regard to the choice of a suitable tuberculin: the adoption of my suggestion always to employ a polyvalent vaccine of both types frees the mind of any anxiety as to whether an appropriate tuberculin is being used (see p. 172). Tuberculin seems to have distinct value in the treatment of tuberculosis of bones and joints, and the clinical condition coupled with the observed reactions is ample guide to dosages and intervals.

Cases seem to do well as a rule on quite small dosages; the initial dose of my tuberculin even for the youngest child may be taken as .00001 c.c.

In tuberculous cases the possibility of mixed infection must always be borne in mind, and not only at the preliminary examination and the beginning of treatment.

(4) and (5) **Chronic Arthritis and Rheumatoid Arthritis.**—As with acute arthritis, so here, a division may be made on bacteriological grounds according as to whether (*a*) the organisms responsible for the condition are localized in the affected joint or (*b*) are localized elsewhere, the joint condition being only a manifestation of bacterial infection of the tissues somewhere. Falling into the first category we have chronic tuberculous arthritis, falling into the second category we have rheumatoid arthritis. Chronic gonococcal arthritis may fall into either category; usually it falls into the second, for positive cultures from the joint fluids in cases of chronic gonococcal arthritis are rarely obtained. According to the best evidence, chronic rheumatic arthritis also falls into the second category. This question is of the utmost importance in vaccine treatment, for unless the bacteriological nature of the infection can be fully and certainly determined, a course of vaccine treatment is a pure gamble. The use of diagnostic doses of vaccine

as mentioned on p. 220 may be of the utmost service; failure to secure a reactive response, within my experience and in my judgment, enabling us to exclude definitely that microbe as being a possible cause of the condition.

Let us assume, in the first place, that a diagnostic dose of vaccine of either the Gonococcus or *Streptococcus rheumaticus* (250-500 millions of the former or 250 millions of the latter) does lead within twelve hours to a definite focal and general reaction, and that in this way a definite diagnosis of chronic gonococcal or rheumatic arthritis has been made. If the reactions were moderate in degree, as is usually the case, nothing is to be gained by reducing the dosage for therapeutic purposes, and treatment is conducted according to the rules already laid down, *i.e.* at the beginning of the course of treatment reinoculation is performed at the first signs of retrogression, not waiting, however, longer than ten days for these to appear; later on, as one becomes familiarized with the responsive powers of the patient's tissues, an effort is made to forestall retrogression by twenty-four to forty-eight hours, if necessary increasing the dosage so that this may be done.

If, however, as is very rarely the case, the focal and general reaction to the diagnostic dose was greater than is considered to be desirable, *i.e.* if a rise of temperature to 103° F. or over, a rigor, vomiting, severe headache, or excessive pain and tenderness of the joint occurred, one should wait till three or four days have elapsed after the complete disappearance of all signs both of the focal and general reaction, and reinoculate with a dose of only one-fourth the magnitude of the diagnostic dose, and thereafter continue on the usual lines.

In the event of the case falling definitely into the

second category, and no response being obtained to diagnostic doses of such vaccines as we consider appropriate to the case, the only thing that can now be done is to make a most careful and methodical survey of the patient for all possible foci of bacterial infection, and each one discovered must be subjected to a detailed bacteriological investigation. Thus the mouth must be searched for carious teeth, pyorrhœa, tonsillitis, and naso-pharyngeal catarrh, the ears for the presence of otitis media, the lungs and especially the bases for chronic bronchitis and the foci I have described on pp. 62, 163, the urethra for gleet, the bladder for cystitis, the kidneys, vagina, and uterus for any chronic inflammatory condition, the abdomen for evidence of dilated stomach, colitis, enteritis, or intestinal stasis. In the event of one or more of these conditions being detected, it is not lightly to be assumed that therein we have necessarily discovered the origin of the chronic arthritic condition, for in many individuals several of these may co-exist without any accompanying joint affection. The clinical history must be gone into carefully and the attempt made to correlate the two conditions. The patient should be informed of the experimental nature of the work, and warned that failure may attend even a very considerable expenditure of time and money.

Sometimes, of course, the case is apparently a simple one from the beginning, as, for example, when the only discoverable focus of infection is indicated by the presence of small quantities of albumen and considerable numbers of streptococci in the urine. Here it would be perfectly justifiable to connect the two conditions, prepare a vaccine of the streptococcus and give a diagnostic dose thereof, smaller, however, than that usually given, owing to the presence of the nephritis. But

when the only associated pathological condition discoverable is such a one as pyorrhœa, mucous colitis, or chronic endometritis—conditions whereof the bacteriology is complex and as yet but imperfectly elucidated—the difficulty in applying vaccine treatment becomes so great as to render the result highly speculative.

Just as the search for a microbe or microbes to which specific action in the production of rheumatoid arthritis can be attributed has proved fruitless, so with these various conditions. Only in rare instances does the bacterial flora fail to be very complex, and the difficulty in assigning their respective rôles to each variety of microbe present is practically insurmountable in the present state of knowledge. The bacteria are as a rule of low virulence to man, rarely induce the formation of any antibodies, and commonly are devoid of pathogenicity towards the lower animals. We also know that bacteria growing symbiotically exercise a powerful influence upon each other's powers of resistance, rate of growth, virulence, and pathogenicity, so that a microbe without direct influence upon the human economy may yet powerfully influence another variety which does produce marked effect upon the tissues. It thus becomes theoretically of doubtful wisdom to press too energetically our search for a specific cause either of the primary or secondary condition, and the results of clinical experience confirm this view.

The position with regard to the vaccine treatment of rheumatoid arthritis is then as follows: (1) No one has yet succeeded in discovering a specific bacterial origin for the disease, either in its acute, subacute, or chronic form. (2) None the less there is little doubt that among the factors concerned in its causation are toxins derived from bacteria resident somewhere in the tissues. (3) The

chronic pathological conditions most commonly associated with it are pyorrhœa, mucous colitis, enteritis, endometritis, urethritis, cystitis, nephritis, and bronchitis. (4) The vaccine treatment of the arthritis therefore consists in the vaccine treatment of the associated primary focus of toxic absorption, and this will be found under its appropriate heading, *vide* pyorrhœa, etc. (5) The clinical results obtained on these lines are sufficiently good to warrant trial of a course of vaccine treatment whenever the existence of one of these diseases can be demonstrated, and more especially when the clinical history proves that it was antecedent to the arthritis. It must, however, be mentioned that at times gout and the so-called uric-acid diathesis seem to be closely associated with the rheumatoid condition. (6) While at the commencement the vaccine therapy must be the more especially directed towards the cure of the primary focus, treatment must be continued for some time after this result has apparently been obtained, and a considerably higher scheme of dosage must then be followed. This is only in accordance with the practice that has been found to yield the best results in chronic arthritic cases with which we can connect a specific bacterial agent, such as the gonococcus, *Streptococcus rheumaticus*, or tubercle bacillus. In these cases the appropriate initial dosages are 100 millions gonococci, 50 millions *Streptococcus rheumaticus*, and .0001 c.c. of tuberculin. The control of subsequent dosages and intervals lies as usual in the careful observation of the reactions, focal and general, which are produced. There may be slight swelling, increased tenderness and pain, and some redness in and around the joint, and slight rise of temperature, headache, and feeling of malaise. Unless one or more of these signs of response to the vaccine

is elicited, the dosage is inadequate or the composition of the vaccine incorrect, and until they are produced no sign of definite improvement can possibly be expected. All signs of reaction must be allowed to pass away and a further two or three days elapse before reinoculation is to be performed. If retrogression occur before the seventh day, increase of dosage is indicated, and the attempt should be made so to adjust the dosage that the interval may be extended to a full fourteen days. At the beginning of treatment it may not be easy to adjust the dosage so as to permit of intervals of more than seven days, but as it progresses this difficulty diminishes, and with dosages of 500 millions and upwards intervals of fourteen days without any sign of retrogression can usually be employed. With gonococci the ultimate dosage should not be less than 2,000 millions—4,000 or even 5,000 millions may be reached ; with *Streptococcus rheumaticus* not less than 1,000 millions, and if 2,000 millions can be attained so much the better. This is the only way in which risk of relapse can be appreciably reduced. For the treatment of those cases in which primary foci elsewhere are discoverable the reader is referred to the appropriate heading.

Goadby (*Lancet*, March 11th, 1911, etc.) attaches especial importance to the streptococci isolated from pyorrhœic pockets, and gives the following table of results : number of cases, 22 ; cured, 12 ; improved, 6 ; no improvement, 4.

Warren Crowe claims to be able to isolate a staphylococcus, which he calls *Staphylococcus deformans*, from the urine in most cases, and to obtain uniformly good results by the use of its vaccine.

Veitch (*Journal of Vaccine Therapy*, vol. i. No. 10, p. 269) combines the *Streptococcus rheumaticus* with

other streptococci, *B. coli* and coliform bacilli, staphylococci, etc., derived from primary foci of infection, and in the paper referred to gives his results as: total cases, 27; greatly improved, 13; improved, 8; no better, 7.

Other observers, working on the lines I have described, claim equally good results, so that it would appear that very material benefit, often amounting to complete arrest of the disease and greatly increased comfort and mobility of the joints, is to be expected in at least 50 per cent. of cases subjected to a sufficiently long course of treatment with the appropriate vaccine.

CHAPTER XII

DISEASES OF THE INTESTINAL TRACT

Disease or organ.	Associated organisms.
Gingivitis, pyorrhœa, follicular tonsillitis, and granular pharyngitis .	Streptococcus, staphylococcus, pneumococcus, <i>B. influenzæ</i> , spirilla, spirochætes, diphtheroids, anaerobes, fusiform bacilli, etc.
Acute tonsillitis . . .	Streptococcus, staphylococcus, pneumococcus, <i>B. diphtheriæ</i> , diphtheroid bacilli, fusiform bacilli, spirilla, spirochætes, and vibrios
Salivary glands . . .	Streptococcus, staphylococcus, pneumococcus
Stomach and duodenum .	<i>B. coli</i> , streptococcus, pneumococcus, <i>B. proteus</i>
Liver and gall bladder .	<i>B. typhosus</i> group, <i>B. coli</i> group, streptococci, spirochæta ictero-hæmorrhagica, etc.
Pancreas . . .	<i>B. coli</i> , streptococcus, staphylococcus
Small intestine . . .	<i>B. typhosus</i> and allies, <i>B. coli</i> and allies, <i>V. cholerae</i> , streptococcus, <i>B. dysenteriæ</i> , <i>B. proteus</i> , <i>B. tuberculosis</i> , anaerobes, etc.
Large intestines and appendix	<i>B. coli</i> , streptococcus, <i>B. dysenteriæ</i> , pneumococcus, <i>B. pyocyanus</i> , <i>B. tuberculosis</i> , anaerobes, etc.
Peritoneum . . .	<i>B. coli</i> group, <i>B. typhosus</i> group, streptococcus, staphylococcus, gonococcus, pneumococcus, <i>B. pyocyanus</i> , <i>B. tuberculosis</i> , anaerobes, etc.

THE most important pathological conditions of these parts having a bacterial origin, and with which I propose to deal, are: (1) pyorrhœa ; (2) sprue ; (3) tonsillitis and inflammation of the salivary glands ; (4) typhoid ; (5) dysentery ; (6) cholera ; (7) gall stones, pancreatitis, diabetes, and infective jaundice ; (8) mucous colitis ; (9) appendicitis ; (10) peritonitis.

Before particularizing it is perhaps well to mention certain broad characteristics more or less common to all bacterial diseases of the digestive tract. Of these the most important from the vaccine point of view are:

(1) The frequency with which various anaerobes are associated with the pathogenic aerobes. Beyond the facts that these two groups each exercise a most powerful influence upon the growth and vitality of the other, and that the products of anaerobic growth are usually extremely toxic to the human tissues, little is known regarding the rôle played by these anaerobes. It may also be mentioned that their activities are greatest at the two opposite ends of the intestinal tract.

(2) The great diversity of organisms which may initiate most of these conditions, necessitating obviously the greatest possible care in diagnosis of the responsible agents.

(3) The fact that most of the species of bacteria concerned are comprised of several closely allied members, and the more minute the scrutiny to which each species is subjected the greater is found to be the number of its constituents. For instance, not many years ago the *B. typhosus* was considered to be the invariable cause of typhoid fever ; now we know that it has close allies in the paratyphoid bacilli A and B. The *Vibrio cholerae*, similarly, is now known to be only the dominant member

of the cholera group. The Kruse-Shiga bacillus of dysentery, also, has close relatives in Flexner's bacillus, the Y. bacillus, Strong's bacillus, and others. Obviously if vaccine treatment is to be rightly employed in such cases, an exact diagnosis of the offending microbe is an essential preliminary.

(4) Pure infections hardly ever occur, complex mixed infections being almost a universal rule. Even in such a case as that of typhoid fever caused by the *B. typhosus*, certain well-known and really thoughtful bacteriologists express grave doubts as to how far the typhoid bacillus is actually responsible for the symptoms associated with the disease and commonly attributed to that bacillus. They point out that the intestinal *B. coli* and streptococci are always associated with the *B. typhosus* in the characteristic lesions, and ask how much we really know of the pathogenic action of this bacillus, and how many of the symptoms are really due to the associated organisms. In prophylaxis this question is not of much moment, in therapeutic inoculation it is of very great importance.

(5) In most of the diseases under consideration the area of infection is very considerable; in typhoid fever there may be 20 ft. of infected small bowel, in dysentery 6 or 8 ft. of colon. The amount of toxic absorption may thus be so great as to render the toxæmia of paramount importance. At the same time the greater proportion of the infecting microbes may be resident rather upon the surface of the tissues than within them; it thus comes about that while the toxins may be readily absorbed into the tissues, the antibodies in the latter have little chance of reaching the bacteria.

The vast numbers of bacteria concerned in the lesions cannot be without some bearing upon the question of

dosage of vaccine required to combat them, and to this point little or no attention has ever yet been directed. To me it seems elementary logic that if the dose of vaccine required to combat the bacteria in a small circumscribed focus of infection be a small one, the dose of vaccine required to incite antibody formation in an amount adequate for the combating of the bacteria in a vastly greater area of infection must be a considerably greater one. Furthermore, while a few living bacteria lead to the production of a limited amount of antibodies, they also produce but little toxin, and so do but little damage to the tissue cells of the body, which accordingly remain in a condition capable of responding well to the stimulus given by a small dose of vaccine; whereas when the infected area is large, the stimulus thus already given to antibody formation is considerable, the amount of toxin formed is large, the resultant damage to the tissue cells great; these latter, therefore, will require the considerable stimulus afforded by a large dose of vaccine if they are to be incited to the elaboration of a further quantity of antibodies.

So far as I am aware no bacteriologist has ever considered the question of appropriate dosages from this point of view, but clinical experience lends some support to its accuracy, and further consideration may well induce us to employ yet larger dosages than even the most enterprising have been wont to use. I know of more than one instance where military doctors in the press of work have given doses of 1,000 and 2,000 millions of antityphoid vaccine in cases of typhoid fever, instead of the 50 or 100 millions dose of typhoid vaccine which they had intended to use. In each case their mental disquietude has been promptly relieved, for, instead of the ill effects they apprehended, the only result they

could detect was speedy improvement in the patient's condition.

(6) As I have already pointed out, toxæmia is usually a very prominent symptom in acute infections of the intestinal tract. Now, the administration of a vaccine rarely leads to the speedy production of antitoxin in any such amount as to be of material benefit to the patient ; the toxic symptoms need combating in a more rapid and adequate manner. The elimination of toxin must be assisted in every possible way, its dilution helped by injections of saline solution, either into the veins or rectum, its neutralization brought about by the administration of serum rich in the appropriate antitoxin whenever such a serum is available. Unfortunately this is not always the case : a good antidysenteric serum has been made, but an efficient antityphoid or anticholera serum has not yet been prepared. Such a serum must necessarily have a high content of antitoxin, and agglutinins are probably of material benefit. A high content of lysin, on the other hand, may be most injurious to the patient, the sudden setting free of endotoxin from the lysinized bacilli being an element of considerable danger. The ideal treatment of a case of, say, acute bacillary dysentery would be :

(1) Immediate neutralization of all circulating toxin by the intravenous administration of antitoxic serum, which requires to be given in a quantity lying between certain extremes—if too little be given, the toxin will not all be neutralized ; if too much be given, the combination of toxin and antitoxin may be inhibited. It would be of a material advantage if makers of sera would in future always indicate the limits between which lies the appropriate dosage for the average case.

(2) The dilution of toxin subsequently formed and

the restitution of the fluid lost per rectum by the injection of large quantities of normal salt solution.

(3) Promotion of the elimination of toxin by skin and kidneys.

(4) The combat of the bacterial infection by the administration of vaccine, best of the sensitized variety, in adequate dosages, for antitoxic sera have very little influence in bringing about the death of the invaders.

(I) **Gingivitis, Pyorrhœa, Follicular Tonsillitis, and Granular Pharyngitis.**—A considerable variety of bacteria are capable of causing these conditions. Very rarely is it possible to assign the predominant rôle to any particular variety of microbe: mixed infections are the rule, and anaerobes are frequently found associated with the aerobes. A streptococcus, usually of the short-chain variety, is perhaps the microbe most commonly found; the *M. catarrhalis* is also found in the majority of cases. Pneumococci, *B. influenzae*, diphtheroid bacilli, spirilla, the *B. fusiformis*, and spirochætes are also frequently present. No attempt should ever be made to take cultures for the preparation of a vaccine without prior cleansing of the superficial structures as much as possible, and the specimens should always be taken from the deeper parts when possible. It should be remembered that toxic absorption from these parts is frequently much greater than could possibly be anticipated from the apparent area of tissues involved. In my opinion, vaccine treatment of these conditions is absolutely contra-indicated until all appropriate measures have first been taken by dentist and surgeon. Vaccines are given no chance whatever when employed in cases where deep pyorrhœic pockets and tonsillar crypts and follicles are left untreated; once these have been dealt with the vaccine has a real chance of dealing with the microbes.

in the deeper parts, diminishes considerably the risk of recurrence, and materially improves the clinical condition of the patient—for it must be remembered that the bacteria of pyorrhœa are those mainly responsible for infective disorders of the stomach and duodenum and certain chronic arthritic disorders (see p. 224).

Some years ago I prepared vaccines of some of the anaerobes commonly found in pyorrhœa and follicular tonsillitis. They proved to be so intensely toxic that I made little use of them; in the few cases where they were employed they did not seem productive of much benefit. Goadby (*Lancet*, September 30th, 1916, p. 585) subsequently tried the effect of 10-20 millions doses of vaccine of *B. perfringens* in eight septic wound cases; in three of these there were produced severe focal reactions, and he found the vaccine of doubtful utility.

In view of the dependence of the anaerobes upon the aerobes for their power of growth, it seems better practice to devote one's attention to bringing about the extinction of the aerobes. In this vaccines certainly can assist.

The limited areas of tissues involved would, according to the theory laid down on p. 231, indicate that relatively small initial dosages should prove efficient, and clinical experience bears this out. At the same time high ultimate dosages are often necessary to prevent relapse. Appropriate initial dosages are as follows: streptococci, 25 millions; pneumococci, 25 millions; *M. catarrhalis*, 50 millions; diphtheroids, 50 millions; *B. influenzae*, 100 millions; staphylococcus, 250 millions. Subsequent dosages and intervals will be controlled by the focal reaction and clinical symptoms; with these small dosages intervals of seven days are usually suitable.

Pyorrhœa has been the happy hunting-ground of

many adherents of vaccine treatment, and most claim to have secured very satisfactory results. Personally, I regard the disease itself as lying much more within the dentist's sphere, and find vaccine of the most value in preventing relapse and in the treatment of conditions such as rheumatoid arthritis, sprue, and infective gastritis when these take origin in a precedent pyorrhœa.

(2) **Sprue.**—The only comprehensive study of the value of vaccines in cases of sprue is that by Sir Leonard Rogers (*Indian Med. Gaz.*, April 1918, p. 121). He came to the conclusion that sprue always originated in a coexistent pyorrhœa and that the streptococcus was the responsible microbe. In this paper he gives a full account of his results in nineteen cases, two of which remained perfectly well for over three years after the conclusion of treatment. His initial dosage is 50 millions; if the reaction is slight or absent, as is almost always the case, 100 millions is given after five days and repeated weekly until there is little or no reaction, when it is increased to 150 millions, and eventually, if necessary, to 200 millions at ten-day intervals. The injections have usually to be continued for from three to six months in typical cases, and occasionally for longer, with intervals of omission. The signs of a reaction are a slight increase in the number and looseness of the daily stools for two to three days, followed by diminution in the number, looseness, and offensive character, and improvement in the colour. The results obtained in some of the cases of this very chronic and distressing malady are most striking; one patient gained 3 st. 10 lb., another 2 st. 7 lb., and yet another 2 st. 1 lb. in weight.

He tabulates his results as follows. By "cure" he means complete absence of symptoms for a year and upwards

after the cessation of treatment, by "greatly improved" cessation of diarrhoea and disappearance of mouth symptoms accompanied by great improvement in the general health, but in which the recovery is not known to have persisted for a year.

	Total	Cured.	Greatly im- proved.	Im- proved.	Not im- proved.	Dead.
Vaccine cases before 1917	13	7	4	—	1	1
,, ,, of 1917.	6	—	3	3	—	—
Total vaccine cases	19	7	7	3	1	1
Former hospital cases.	45	—	5	8	26	6

Rogers concludes that the results of the vaccine treatment show a vast improvement on former lines of treatment as illustrated by the large hospital series.

(3) **Acute Tonsillitis and Inflammation of the Salivary Glands.**—Acute tonsillitis due to the fusiform bacillus has assumed an epidemic form in many camps, and will probably reappear in civilian life. Fortunately it is so amenable to local treatment with salvarsan or with liq. arsenicalis and vin. ipecac. that vaccines are not necessary.

Streptococcus, pneumococcus, and of course *B. diphtheriae* are the common aerobes setting up inflammation of these parts. The last of these is so amenable to serum treatment that only very rarely is a vaccine called for. It may, however, prove decidedly useful in those cases where the infection persists long after all clinical symptoms have disappeared, and where there is real danger of the patient becoming a carrier. Several cases are on record where vaccine treatment has brought about the rapid disappearance of the microbe. For a young child an initial dosage of 5-10 millions according to age, for an adult one of 25 millions is appropriate.

In acute infections by the streptococcus, staphylococcus, or pneumococcus general measures or surgical

interference usually suffice. Should these fail, trial may be given to the vaccine in initial dosages of 25 millions of streptococcus and pneumococcus and 100 millions staphylococcus. Fuller trial than heretofore might well be made of vaccine in cases of quinsy, which seem to be especially well suited to this treatment.

I have had one interesting case of infection of the salivary glands with *Streptococcus longus* giving rise to the most intense and distressing salivation. Its early history, ending so far in failure, is fully recorded on p. 201, *Vaccine Therapy*, Fourth Edition. I am pleased to say that complete and lasting cure was ultimately obtained with the vaccine in final dosages of 250 millions.

(4) **Typhoid Fever** (for prophylaxis see p. 71; carriers, see p. 120).—A very extensive literature indeed has accumulated regarding the vaccine treatment of typhoid fever. Much of it has been devoted to advancing the claims for recognition of various special vaccines, for which there is no call or need whatever: the ordinary vaccine or a sensitized one is all that is needed. The amount of toxic absorption from the great area of tissue involved is so very considerable that the additional toxin introduced with such colossal doses as are never used would probably be quite negligible. The bulk of the literature is, however, concerned with treatment by means of dosages which are utterly inadequate to incite antibody formation by tissues already heavily laden with toxin and needing stimuli of considerable magnitude. As I have already mentioned, doses of 1,000 and 2,000 millions have been given without producing any undesirable reaction. I am convinced that the vaccine treatment of typhoid fever has been based on quite erroneous premises, and that probably no investigator has yet recognized the true problem before him or given

adequate dosages. The majority of workers have based their dosages as if the disease when fully developed were essentially a septicæmia. Only at the very beginning does the disease partake of a septicæmic nature, the more important condition being a large area of tissue more or less superficially infected by the *Bacillus typhosus*. "Septicæmic" dosages may then be justified, but I consider that a much more liberal scale is expedient. Later on, as the tissues become more deeply infected, we have to deal with a huge area of toxic absorption and the main call is for an efficient anti-endotoxic serum; which unfortunately does not yet exist. If it did, its administration, followed, when the toxin had been neutralized, by moderate doses of vaccine, preferably sensitized, would be the appropriate treatment. Yet later in the disease we have to deal with a great area of tissue, deeply infected, not only by the *B. typhosus*, but also by the *B. coli* and *streptococcus*. The tissues by now are developing considerable quantities of antitoxin, agglutinin, lysin, and opsonin to the *B. typhosus*, but bactericidin which will kill the bacteria appears to be in defect, and as to how the tissues are reacting to the *B. coli* and *streptococcus* we have no information. If vaccine is now to be used—and it should prove of material service in leading to the extinction of the infection, and so reducing the risk of haemorrhage and relapse—it should be a compound one of the three organisms and given in full amount with due regard to the great area of tissue involved. I am not at all convinced that it would not be of more value in the early stages to give a vaccine of *B. coli* and *streptococcus* to raise the immunity against these organisms to a high level before they begin to take a very active part in the process of destruction of the tissues, than it is to give

a vaccine of the *B. typhosus*. However this may be, if a vaccine of this last be given in the early stages, vaccines of the other two should certainly be included.

I have collected all the available statistics of vaccine treatment in typhoid fever, whether the initial dosages were 50 or 500 millions, and added them together. The mean mortality rate per 100 works out at just 4 against the ordinarily accepted rate of 15 per 100; the mean percentage of relapses works out at 3.7 against a generally accepted rate of not less than 20. The unanimous conclusion is that vaccines are quite innocuous and produce no undesirable reaction, but that, on the contrary, they confer distinct benefit, shortening the pyrexia and duration of the disease, diminishing toxæmia, and reducing both the mortality and liability to relapse.

The tendency of each worker has been materially to increase his initial dosages as his experience grew. The best results have been obtained by Semple and Callison, the former using initial dosages of 100 millions, increasing to 200 and 300 millions, given daily or on alternate days under the guidance of the clinical symptoms. Callison used initial dosages of 300 millions, and takes agglutinin estimations as his guide.

A consideration of the literature brings out clearly that initial dosages of not less than 250 millions can be safely used and that these are to be repeated or increased under the guidance of the clinical signs and symptoms.

Ranque and Senez (*Anales de la Facultad de Medicina Montevideo*, October and November 1917) employ a vaccine sterilized by addition of .03 per cent. of iodine, which they state is devoid of all toxicity. They gave doses of 250-1,000 millions, and endeavoured to incite

a slight febrile reaction which they claim is followed by defervescence, the course of the disease being always favourably modified, duration being shortened, and complications and relapses entirely suppressed.

(5) **Dysentery** (for prophylaxis see p. 82 ; carriers, see p. 119).—The theoretical considerations I entered into on p. 230 with regard to typhoid fever hold with equal or even greater force with regard to dysentery, with, however, one or two modifications : (1) Toxæmia assumes an added importance, but fortunately an efficient anti-endotoxin to the Kruse-Shiga bacillus, the most toxic member of the family, is available, and in doses of 50-100 c.c. is productive of great benefit. (2) The somewhat mythical toxicity of the typhoid vaccine is here replaced by a very real toxicity in the case of the Kruse-Shiga bacillus ; vaccines of Flexner's bacillus and the other allies do not present this difficulty. As mentioned on p. 45, a great amount of work has been devoted to the preparation of an atoxic Shiga vaccine, and Broughton Alcock, Gibson, and myself have apparently had complete success. My own vaccine has been used on less than a dozen cases of acute dysentery, in initial doses of 100 millions, so it is not possible to estimate its value in treatment. It certainly produced no undesirable reaction and no ill-effects, and the impression was that it materially benefited the patients. It is at least worthy of a thorough trial. As regards Gibson's and Broughton Alcock's vaccines, I am not in possession of any statistics.

The most extensive experience of the use of vaccines in bacillary dysentery, both of the acute and chronic form, is that of Major W. H. C. Forster, who used an admittedly toxic vaccine of the Kruse-Shiga bacillus for the treatment of all cases, whether by that organism,

Flexner's bacillus, Strong's bacillus, or Bacillus Y. of Hiss. He claimed uniformly successful results (*Indian Med. Gaz.* June 1907, p. 201). Thus of ten chronic relapsing cases, seven remained perfectly well for twelve months after treatment. Shivdas (*Journ. of Vaccine Therapy*, vol. i. No. 4, p. 112) on similar lines achieved considerable success, especially in the chronic relapsing cases, for which all medical treatment had proved unavailing. Forster's vaccine has to be standardized by animal experimentation, and is not obtainable in this country. It is too toxic for routine use in acute cases, and it would seem advisable in these cases to use the vaccine made by Gibson or myself.

As to how Gibson would propose to use his I cannot say; my own is perfectly safe in initial dosages of 150–200 millions, and contains all the common types of dysentery bacilli.

Subsequent dosages and intervals are to be controlled in the usual manner, *i.e.* by the clinical signs and symptoms. If the initial dose produce no reaction within twenty-four hours, it may be repeated or increased in another twenty-four hours. When the effective dosage has been ascertained, it should be continued and the attempt made to forestall any signs of retrogression. This will probably mean intervals of between three and five days' duration.

Ross and Kennedy (*Lancet*, June 23rd, 1917, p. 965) have made an extensive trial of dysentery vaccine on West African natives. The vaccine they used was composed of six strains, viz. Shiga, a para-Shiga, Flexner, and three different strains of Morgan's bacillus. Each of these was grown for three days in peptone broth at 37° C., and sterilized by the addition of 0.4 per cent. carbolic acid. Equal parts of these six vaccines were

mixed together; they were not standardized. The usual initial dose was 1 c.c. of the mixed vaccine. On the eighth day 2 c.c. were given, on the fifteenth 3 c.c., and if necessary on the twenty-second day 4 c.c.

They say no toxic symptoms developed, and that their results in 350 cases, which will be fully recorded later, were very satisfactory. Whether there is anything peculiar in the West African native I know not, but I am certain that white sufferers from acute dysentery will not tolerate anything like such dosages of ordinary broth cultures.

Asylum dysentery and the summer diarrhoea of children both offer good opportunities for the employment of vaccine treatment. Small series of cases have been so treated with uniformly satisfactory results. In these cases it would always be wise to have an auto-gogenous vaccine made; usually one type of organism is responsible for the epidemic, but if two or more are found a polyvalent vaccine can easily be prepared, and in this way quite possibly the more toxic Shiga strain may be appropriately excluded from the vaccine. In the case of Gibson's or my own vaccine, this is not necessary, but in these possibly an uncommon strain responsible for the given epidemic may not be included.

(6) **Cholera** (for prophylaxis see p. 78; carriers, see p. 122).—Vaccines so far have played no part in the therapeutics of this disease.

(7) **Gall Stones, Infective Jaundice, Pancreatitis, and Diabetes.**—In the production of these conditions bacteria may play a chief or a subsidiary part, the bacteria being carried to the parts by the blood stream or passing directly up the ducts from the duodenum. Cultures of gall stones extracted by operation have yielded pure growths of the *B. coli* and *B. typhosus* groups. Culture

of the liver and bile in cases of infective jaundice especially from Gallipoli have yielded pure cultures of the *B. typhosus* group, and especially of the paratyphoid bacilli. Diabetics are notoriously susceptible to attacks by the staphylococcus and *B. coli*, and cultures from the pancreas in cases of pancreatitis have yielded cultures of the same microbes. There is accordingly a definite scope for vaccine treatment in all these conditions, even if it takes a secondary part to the lead of the surgeon. The suggestion of Wright (p. 111) may well be followed in cases for operation, which may receive one or more prophylactic doses as there described. After operations for gall stones, it would be a wise procedure always to have cultures made from the centre of the stones. A short prophylactic course twice a year would then tend materially to reduce the risk of recurrence. Where suppuration ensues after operation, a vaccine of the organism or organisms found will yield the surgeon material assistance in hastening the closure of the fistula.

In cases of infective jaundice with a recent history of typhoid fever, trial may well be given to full therapeutic doses of the various typhoid bacilli, say initial doses of 100-250 millions of each.

As the fact has been established that *B. coli*, staphylococcus, and streptococcus are frequently associated with cases of pancreatitis, a compound vaccine of these intestinal organisms is well worthy of a thorough trial.

The connection between diabetes and microbial infection is well seen in the cases recorded by Shivdas (*Journ. of Vaccine Therapy*, vol. i. No. 4, p. 100), Miller (*ibid.* vol. i. No. 5, p. 157), and MacWatters (*Proc. Roy. Soc. of Medicine*, vol. iii. No. 9, Supple-

ment p. 178). In thirteen cases a vaccine of *Staphylococcus aureus* prepared either from a carbuncle or diabetic ulcer was given in doses of 100 to 500 millions at intervals mostly of seven days, but varying from three to ten days.

The results may be tabulated thus:

Observer.	Dose and Intervals.		Duration of Treatment.	Effect on Sugar.
	Millions.	Days.		
Shivdas	100-300	8	2 months	4% disappeared.
	150-250	8	40 days	4% disappeared.
	125-250	6, 10, 15	6 weeks	3% fell to $1\frac{3}{4}\%$.
	250-500	8	2 months	$2\frac{1}{2}\%$ disappeared.
	100-250	10	3 "	4% fell to 1%.
Miller	250-1,000	7	2 "	abundance disappeared.
	250-5,000	7	1 month	? amount disappeared.
	300	7	1 "	considerable amount disappeared.
Mac-Watters	200	7	3 weeks	2% disappeared for six months, then 0.5%.
	300-500	7	3 months	9% fell to a trace.
	250-500	5		16 ounces fell to 2 ounces—death.

They are sufficiently striking to show that material benefit may be conferred on certain diabetics by the administration of a vaccine of *Staphylococcus aureus*, and I would suggest that with the addition of an auto-gogenous vaccine of *B. coli* even better results might be achieved.

(8) **Mucous Colitis.**—In a few typical cases of this disease I have been given every opportunity to effect a cure. When with thorough medical treatment I had done all I could do, I had resort to vaccines prepared as I thought with the utmost care and discrimination from the

shreds of membrane. I regret to say that in my hands they entirely failed to produce the least further improvement, and for several years I have abandoned their use in the disease. I am the more disappointed in that I can see no sound reason why they should have so utterly failed me, as Butler Harris (*Proc. Roy. Soc. of Med.*, vol. iii. No. 9, p. 104), Eyre (*ibid.* p. 63), Willcox, Matthews, and others claim to have had a certain measure of success.

Butler Harris uses doses of 10 millions of *B. coli* at weekly intervals, and the others follow much the same plan. They all agree that vaccine treatment should be given a trial before resorting to any operative procedure. The initial doses of the intestinal organisms which may be tried are 10 millions *B. coli* and streptococcus and 100 millions staphylococcus, as used by the above, who have had some success. Personally, I should be inclined to use a very greatly increased dosage, especially if this one failed to effect improvement.

(9) **Appendicitis and Peritonitis.**—In cases of recurrent appendical pain where operation is contra-indicated or refused by the patient, trial may well be made of a composite vaccine of the intestinal aerobes, *B. coli*, streptococci, and staphylococci in initial dosages as given for mucous colitis. In cases with a history of typhoid fever or dysentery, the appropriate microbes may be included in the vaccine. Crofton (*Therapeutic Immunization*, pp. 98 and 99) says: “Vaccines from these sources will permanently cure mild cases of appendicitis and remove the necessity, at present generally recognized, for operation during the quiescent period.” This strikes me as a bold claim, but I do not know the evidence upon which he bases it. I should hardly care to state the position so to any patient of my own, but if

he were averse from operation, I should certainly be prepared to give the treatment a trial.

In operative cases, especially where an abscess or fulminating appendix is found, the case is quite different. I feel it is the surgeon's elementary duty—in which, by the way, he often fails—to have cultures made at the time of operation, so that a vaccine may be ready in case complications arise. Indeed, the wiser course is not to wait for trouble, but to begin treatment with small doses, such as 10 millions *B. coli* or streptococcus and 100 millions staphylococcus, as soon as the patient has recovered from the operative shock. If this course were followed by all surgeons as a matter of routine, I have not a shadow of doubt that many lives would be saved and that the period of convalescence would be materially reduced.

If this precaution be neglected and peritoneal infection occur, the difficulties of vaccine treatment are increased by any further operative procedure and even by such necessary steps as an evacuation of the bowels, for thereby auto-inoculations of unknown magnitude are produced. The conduct of such a case is precisely similar to one of septicæmia (p. 175). A sensitized vaccine should be given preference over an unsensitized one.

Chronic peritonitis is commonly due to the tubercle bacillus, and in young children the bovine type is probably responsible. Vaccine treatment is of undoubted benefit ; the wiser course is to use the mixed human and bovine types, and polyvalent tuberculin "M" mixed may be given at weekly intervals, beginning with a dosage of '0001 c.c. As neither focal nor constitutional reaction is likely to be noticeable, a purely empirical scheme of slowly increasing dosages at intervals of seven to ten days must be adopted.

In women the possibility of the gonococcus being responsible for a condition of either acute or chronic peritonitis should always be remembered. If the clinical history fail to throw any definite light upon the case, and pathological material, suitable for examination, be not obtainable, trial may be made of a stock polyvalent gonococcus vaccine in initial dosages of 50 millions. If a characteristic reaction, focal or general, be obtained, this will go far to confirm the provisional diagnosis ; if no reaction result from the dose of 50 millions, higher ones of 100 and 250 millions should be given a trial, as no harm can result in the absence of a reaction.

CHAPTER XIII

DISEASES OF THE GENITO-URINARY SYSTEM

Disease.	Organisms associated therewith.
1. Pyelitis and nephritis (acute)	<i>B. coli</i> , <i>streptococcus</i> , <i>pneumococcus</i> ; <i>staphylococcus</i> , <i>B. proteus</i> , <i>B. pyocyaneus</i> , etc.
2. Pyelitis and nephritis (chronic)	<i>B. tuberculosis</i> (primary), above organisms as secondary invaders. Also <i>B. coli</i> , <i>B. typhosus</i> as primary
3. Cystitis (acute) . . .	As for (1) with addition of <i>gonococcus</i>
4. Cystitis (chronic) . . .	<i>B. coli</i> , <i>B. tuberculosis</i> (primary), as for (1) secondary
5. Urethritis, orchitis, epididymitis, vesiculitis (acute)	<i>Gonococcus</i> , <i>staphylococcus</i> , <i>streptococcus</i> , <i>B. coli</i>
6. Urethritis, orchitis, epididymitis, vesiculitis (chronic)	<i>Gonococcus</i> and <i>B. tuberculosis</i> (primary), <i>staphylococcus</i> , <i>streptococcus</i> , <i>pneumococcus</i> , <i>B. coli</i> , <i>B.</i> of Friedländer, <i>B. proteus</i> , <i>B. influenzae</i> , etc. (secondary as a rule, but occasionally primary)
7. Vulvo-vaginitis (acute) .	As for (5)
8. Vulvo-vaginitis (chronic) .	As for (6)
9. Metritis, endometritis, and salpingitis (acute)	As for (5)
10. Metritis, endometritis, and salpingitis (chronic)	As for (6)

So far as the urinary tract is concerned, the commonest cause of acute infections is the *B. coli* group, of chronic infections the *B. tuberculosis* and *B. coli* group. As

regards the genital tract, the commonest cause of acute infection is the gonococcus, of chronic the gonococcus and *B. tuberculosis*. In acute infections of the genito-urinary system, simple infections are by no means uncommon, but unless direct smears are carefully studied, danger of missing a double infection is always present when the *B. coli* is the principal invader, as this organism is such a free grower that it rapidly outgrows other organisms like the streptococcus and pneumococcus. I well remember one case which two bacteriologists had vainly tried to cure with a vaccine of *B. coli*. In examining direct smears I found one streptococcus to every ten or twenty *B. coli*. By making cultures in a mixture of equal parts peptone broth and a strongly agglutinating *B. coli* serum, I was able to isolate the streptococcus within twelve hours, and with the combined vaccine of *B. coli* and streptococcus cure was rapidly effected.

In chronic infections of the genito-urinary tract, a simple infection is a great rarity, whether the primary invader be *B. tuberculosis*, *B. coli*, or gonococcus, and to the omission of examinations of direct smears of specimens taken with the correct technique by far the greater proportion of failures with vaccine treatment is to be attributed. The *B. tuberculosis* will not grow at all with ordinary methods, the *B. coli* tends to out-grow nearly all the other organisms, the gonococcus fails to grow unless special media be employed.

All the potentialities therefore exist for an incorrect or incomplete bacteriological diagnosis of the causative organisms if the examination of smears of the pathological specimen be omitted or carelessly performed. As regards the collection of specimens, the urine should always be procured by means of a sterile catheter; for urethral secretion the first two or three inches of the

urethra should always be thoroughly flushed out with sterile salt solution, and the course of the canal then gently massaged, or preferably the secretion collected from the infected mucosa, duct, sinus, or lacuna on the end of a probe through a Wyndham Powell urethroscope; for prostatic secretion the whole urethra, anterior and posterior, should be thoroughly flushed out, which can only be done when the patient is lying down, the prostate or vesicula massaged per rectum, with the patient in the knee-elbow position, and the secretion collected in a sterile receptacle as it drops from the urethral orifice; for uterine secretion the vagina must be thoroughly flushed with several pints of sterile salt solution, and a guarded probe inserted into the cervical canal with the help of a speculum; for vaginal secretion the specimen may be taken with a swab and speculum, but for myself I prefer a preliminary flushing of the vagina one to three hours before the swab is taken.

If these precautions be observed, not only are contaminations avoided, but the bacteria which are resident simply in the exudate or on the surface of the mucosa, living a purely saprophytic life, are also excluded to a considerable extent, and a representative specimen of the true pathological material is the more readily obtained.

If doctors could only realize how such methods not only facilitate the work of the bacteriologist, but also enable him to arrive at something approaching a correct diagnosis, I feel sure that the number of quite hopelessly unsuitable specimens arriving at the laboratory would be very materially reduced. Needless to say the best and only really satisfactory procedure is to allow the bacteriologist access to the patient and afford him every opportunity for the collection of his own specimens.

For the purposes of applied vaccine treatment the diseases on p. 249 may be grouped into four divisions as follows: (a) acute infections of the urinary tract, excluding the male urethra; (b) chronic infections of the same; (c) acute infections of the genital organs and tract; (d) chronic infections of the same.

In considering bacterial diseases of the **urinary tract**, the first point to be elucidated is whether calculi be present or not, and if they are, whether operative interference is or is not required. If calculi be not present it becomes necessary to consider the mode of origin of the infection: (1) whether it is hæmic, as in the case of nephritis, due to the *B. typhosus*, or the streptococcus associated with scarlet fever; (2) due to an overloaded sigmoid or rectum exercising such continual pressure on the bladder that a mild inflammatory condition is set up, and the *B. coli* and streptococci of the bowel making their way through the intestinal and bladder walls, and setting up the corresponding cystitis; or (3) whether it is due to an enlarged prostate causing retention of urine, which becomes infected from the bowel or elsewhere, thus setting up a primary cystitis, and possibly a secondary ascending nephritis; (4) whether it is due to some temporary cause, such as the presence of a foetus in the uterus pressing on the bladder and inducing retention, the urine as in (2) and (3) becoming infected from the bowel; (5) or whether it is due to some chance occurrence, such as the casual infection of the blood or kidneys when the vitality of the body happens to be lowered through cold, exposure, or starvation, as probably in trench nephritis and the acute nephritis of children. These points need the most careful thinking out, for while a localized infection of the kidney by the *B. typhosus* or *Streptococcus scarlatinæ*, set up

by the bacilli in the blood stream finding a suitable nidus in the kidney tissues, is obviously well suited for vaccine treatment ; and while an acute cystitis, due to the presence of a foetus in the uterus, may be expected to make a natural recovery when delivery has occurred, and if it then fail to do so vaccine treatment may reasonably be expected to conduce to cure : on the other hand, all the vaccines in the world cannot be expected to bring about the expulsion of a calculus embedded in kidney tissue or bladder wall, or to cause any material reduction in the size of a chronically enlarged prostate. Only surgical interference will eliminate these primary causes of the infection, and even if vaccine treatment resulted in the disappearance of the infection, recurrence would be inevitable so long as the prime cause remained.

The doctor may reasonably be expected to pay due regard to these considerations, and not to endeavour to demand from vaccine treatment what vaccine treatment cannot possibly achieve.

When the true clinical condition of the patient has been thoroughly worked out and the nature of the infection accurately determined, it becomes possible to form an exact idea of the services which vaccine treatment may be fairly expected to render. In the first place, if operation is necessary and has been decided upon, a preliminary course of vaccine treatment will (1) diminish the density of the infection ; (2) improve the general condition of the patient, perhaps to such an extent that cases wherein operation is fraught with danger may well be rendered thoroughly fit for operation ; (3) so increase the antibodies present that danger of post-operative sepsis or infection is reduced to a minimum. The suitable initial dosages will depend entirely upon the clinical condition of the patient, and

so vary from those appropriate to a case of septicæmia to those appropriate to pure prophylaxis in a healthy man—*i.e.* between the limits of 25 and 250 millions *B. coli*, *B. pyocyaneus*, or *streptococcus*, of 50 and 1,000 millions *staphylococcus*, and so on. When the operation is over and the patient has recovered from operative shock, the therapeutic administration of vaccines, beginning with moderate dosages, such as 50 millions *B. coli* and *streptococcus* and 250 millions *staphylococcus*, will further diminish the danger of sepsis and infection, and materially hasten the recovery of the patient.

Finally, in cases where operative interference is not necessary, the appropriate initial dosage will depend upon the age of the patient and the general clinical condition. For instance, for a case of **post-scarlatinal nephritis** in a child of ten, where the general condition is not wholly unsatisfactory, an initial dose of 5 millions *streptococci* may be given. An effective response will be evidenced by almost immediate increase in the albumen of the urine, slight rise of temperature, apparent increase in the number of *streptococci* and pus cells in the urine, and perhaps slight malaise, all rapidly followed by a move in the opposite direction, *i.e.* diminished excretion of albumen and bacteria, fall of temperature, steadyng of pulse, and improved clinical condition. If no such reaction occurs within twenty-four hours, the dose may then be repeated, or we may wait another twenty-four hours and give a double dosage. So long as a good response is given to any dosage, no increase should be made. A similar plan should be followed in a case of **acute nephritis of children**, which is said to be usually due to the *B. coli*. I am not at all satisfied that this is the case, but think that *streptococci* are often

concerned in it, either alone or in association with the *B. coli*. In the case of a child, say of five or six years, who does not appear to be making progress, the bacteriology should be carefully worked out, and an autogenous vaccine or vaccines, preferably sensitized, should be administered in initial dosages of $2\frac{1}{2}$ millions unsensitized or 5 millions sensitized of either or both organisms.

I have before me a very careful and detailed account of the results of vaccine treatment of eighteen cases of nephritis in infants, one of them only nine days old, two of them only two weeks old, and all under one year of age. The record came from abroad, I believe South Africa, and unfortunately I cannot decipher the author's name. In eleven of the eighteen cases typical *B. coli* were present, in the other seven sundry variants which did not ferment saccharose or lactose and did not form indol. The dosages and intervals of the autogenous vaccines were controlled in the way I have advised. One case died of broncho-pneumonia, two did not improve, two made great improvement but were not cured, the remaining thirteen made complete recoveries despite the frequent presence of quite serious complications. The initial dosages were high, the lowest being 15 millions in the case of the baby only nine days old; the highest ultimate dosage was 700 millions in one of the cases that showed no improvement. No excessive reaction is stated ever to have occurred. The paper is so well worth study that I greatly regret being unable to give the reference to its origin, some of the temperature charts alone illustrating well the nature of a perfect response to a dose of vaccine.

The nephritis of pregnancy, again, is stated to be almost invariably due to the *B. coli*. I have only this week heard of such a case where streptococci were

present in great numbers alone in the urine, and a *B. coli* vaccine was about to be administered. I could do nothing in the matter, and another failure will be recorded to vaccine treatment !! This nephritis does not always occur during pregnancy; by no means infrequently it appears to begin four to six weeks after delivery, when perhaps the strain of lactation begins to be felt, as in two of four cases of pyelonephritis recorded by Sir Thomas Oliver (*Lancet*, September 25th, 1909, p. 913). Here the pyelitis began six or seven weeks after delivery, as in a case of my own. Weekly injections of vaccine caused gradual disappearance of pyrexia and complete recovery. Oliver considers that "the results achieved by vaccine treatment far outweigh anything likely to be got by internal administrations of medicine."

Morse, after considerable experience, considers that "in the more intense and persistent cases vaccines are the only hope." Like myself, he considers that they should be given in the largest possible dose that will not produce a marked reaction, and would have these repeated every four days. I differ from him in this, that I consider every case has to be treated on its merits, that adequate guides exist as to dosage and intervals, and that a set time for reinoculation should never be made.

I am pleased to be able to record that the final result in the very difficult and tedious case of my own described on pp. 237-9 of *Vaccine Therapy*, 4th edition, was cure, so far as the pyelitis was concerned. The general condition, unfortunately, remained poor, but not so poor, however, as to prevent the lady undertaking another pregnancy, which terminated uneventfully.

The general opinion is that the prognosis is especially bad in those cases where the pyelitis only develops some

weeks after parturition ; and that the only real hope of a happy issue lies in the careful conduct of a course of vaccine treatment.

Acute and Chronic Cystitis.—I have already referred fully to the great necessity of ascertaining the predisposing factor for the infection and dealing with this adequately along medical or surgical lines, before indulging in the hope that vaccine treatment will bring about any permanent cure. I have also referred to the necessity of making an accurate bacteriological diagnosis, of avoiding the hastily formed conclusion that the infection is a simple one, and that the *B. coli* is alone concerned, and I have referred to the use of vaccines as a prophylactic agent before operation, and as a therapeutic one afterwards. Cases not requiring operation, when due regard has been paid medically to the predisposing factors, would appear to present few difficulties in vaccine treatment. Unfortunately this conclusion is not always borne out by results.

For this two things are, I think, mainly responsible : (1) the rather superficial nature of the infection and the difficulty the antibodies experience in attacking the microbes ; (2) the peculiar faculty, especially exhibited by the *B. coli*, and the more especially shown in cases of cystitis, of immunizing itself against the antibodies formed in response to the inoculations. This difficulty is best met by interrupting treatment for a few weeks and then preparing a fresh vaccine.

Cystitis due to lesions of the **central nervous system**, whether these be the result of disease or injuries to the cord, such as those sustained in warfare, is apt to prove little amenable to ordinary medical treatment, and a serious danger to the well-being and even the life of the sufferer. Vaccine treatment, both of the acute and

chronic form, frequently proves of the greatest service, and an occasional prophylactic course in cases in which cystitis has not yet developed may be expected to delay or even altogether prevent the onset of infection. Thomson Walker (*Lancet*, 1917, vol. i. p. 173) has found vaccines of such great value in the treatment of the paraplegic cases at the "Star and Garter" that they "require a chapter to themselves."

In cases of acute cystitis, cure is as a rule so speedy that the difficulty due to the self-immunization of the *B. coli* against the antibodies is not encountered, but in chronic cases, where progress is slow and very high dosages have often to be attained, it sometimes is a source of much trouble.

The control of dosages and intervals will lie mainly in examinations of the urine for albumen, pus, mucus, and microbes; the temperature and pulse chart and general condition of the patient also afford material help.

In cases of acute cystitis initial dosages of 10-25 millions *B. coli*, streptococcus, gonococcus, and pneumococcus, and of 100-250 millions staphylococcus, may be used; in chronic cases these may be doubled.

Cases of chronic infection of the urinary tract by the *B. tuberculosis* are almost invariably secondarily infected by one or more of the bacteria capable of setting up of themselves an acute infection of the part. My invariable practice, and I think it the only logical one, is first to deal with the secondary invaders precisely as if they were the primary ones and upon the lines already laid down, and when these are well in hand and the effective dosages thoroughly worked out, then to deal with the tuberculous infection. If any other course be followed, all control of dosages and intervals is sacrificed. If the albumen or pus temporarily increase, we are quite

at a loss to know whether this is in response to the dose of tuberculin or to the dose of vaccine. With the procedure I advise we are never left in any doubt. Moreover, clinical results fully endorse its wisdom, for cases of renal or bladder tuberculosis respond surprisingly well to this treatment. I have, for instance, alive and perfectly well to-day a patient who was considered by three genito-urinary specialists as past operation six years ago. He has discharged throughout the war duties of an exceedingly onerous and exacting nature, yet when I heard a few weeks ago, he was nearly as heavy as he had ever been in his life, and was feeling fit and well. He had double renal tuberculosis, secondarily infected by streptococcus and an aberrant type of *B. coli*. I began in his case with initial doses of 25 millions *B. coli* and streptococcus, and attained final doses of 1,000 millions of each. The initial dose of tuberculin was .0001 c.c. of my tuberculin "M" mixed human and bovine strains. With this tuberculin final therapeutic doses of 0.01-0.1 c.c. can easily be attained. Focal reactions are always manifested by adequate dosages, and I have never yet seen anything beyond a mild constitutional reaction.

While failures are certain to be met with by every worker, success in the vaccine treatment of diseases of the urinary tract is probably in direct ratio to the skill and care bestowed on the predisposing factors. The best recorded results are those by Wulff (*Presse Medicale*, 1910, p. 97), who claims eighteen cures in twenty-one cases, the other three not being much benefited. Billings considers that improvement can be brought about in all cases by vaccine alone, but that where there is obstruction to the urinary flow entire recovery will not occur until this is relieved.

Emery (*Immunity and Specific Therapy*, p. 394) says: "Vaccine treatment cures all the symptoms and reduces the pus and bacilli to a small fraction of their original amount, but fails to remove them entirely. There is no doubt that the treatment is the best available."

It is obvious with bacteria like the *B. coli* and *streptococcus*, which include so many variants in their groups, that the best results are only to be anticipated from the use of autogenous vaccines, and that when the general condition is bad, sensitized ones are to be preferred. None the less, good results have frequently been obtained from reliable stock vaccines, but with these the question of appropriate dosage needs consideration. For instance, suppose that ten strains are present, and that in a given case only two of these induce the formation of the appropriate antibodies, it follows that the effective dosage is only one-fifth of that indicated as contained in the ampoule. In other words, if a total of 50 millions be given as the initial dose, a dose of only 10 millions of effective bacilli is actually administered.

This fact actually creates no real difficulty when the operator works upon the lines I have indicated, *i.e.* of beginning with a low dosage and gradually increasing it with a view of finding the dosage to which the patient makes an adequate response, unless and until he decides that the stock vaccine is not effective, and that he will try an autogenous one; when it is obviously wise for him to begin with a greatly diminished initial dosage. If, for example, the last dose he gave was 250 millions of the stock vaccine, the first dose of the autogenous one should not exceed 50 millions. This should always be borne in mind when changing from a stock to a polyvalent vaccine in the case of those bacteria which present many variants or different strains.

Acute Infections of the Genital Tract: (a) in men; (b) in women; (c) in children.—In each by far the commonest cause is the **gonococcus**, but I have been for many years convinced that acute non-gonococcal urethritis is a great deal commoner than any textbook on specific diseases would induce one to believe. The period I spent in command of the Venereal Section of the New Zealand Expeditionary Force afforded further evidence of the validity of my view, and Mr. Wyndham Powell, than whom no more reliable authority on gonorrhœa exists in the world, tells me he shares this opinion. Not that non-gonococcal urethritis can be called a common disease, but it occurs with sufficient frequency to render it absolutely unjustifiable for any medical man to diagnose gonorrhœa without finding the gonococcus in smears of the acute discharge. In those under twenty-five years of age it occurs certainly in not less than 3 per cent. of cases, and quite possibly in a considerably higher percentage. As the age of the patient increases, so does the frequency of non-specific acute urethritis, possibly due to the fact that previous attacks of specific urethritis have raised the patient's immunity to the gonococcus, but not to the other bacteria. In patients over forty years of age the non-specific variety is quite common.

I think non-specific urethritis occurs most commonly in those with large organs, especially if these have wide meatus, and that they are the result of coitus with a female either suffering from leucorrhœa or not yet fully recovered from her menstrual discharge. The staphylococcus is undoubtedly the commonest cause, next to this the *B. coli*, and then possibly bacteria closely related to and almost indistinguishable from the *B. influenzæ*. The streptococcus, pneumococcus, and bacillus of

Friedländer are also found occasionally. These cases, and especially those due to the staphylococcus and *B. coli*, sometimes prove very refractory to ordinary treatment, but respond very well indeed to vaccines, initial dosages of 250 millions of the former and 50 millions of the latter being suitable in uncomplicated cases. In cases complicated by prostatitis, vesiculitis, or epididymorchitis this dosage should be halved, for if a local focus of suppuration exist the higher dosage may induce rigors and a severe constitutional reaction. Not that any particular harm will result therefrom ; on the contrary, the presence of a previously unsuspected focus of suppuration may be revealed thereby, for let me impress upon the reader the fact that such a reaction with the dosage recommended is absolutely diagnostic of pus under pressure, and cannot be referred to any other cause. I remember a case I attended with Mr. John Pardoe which illustrates this well. The patient was suffering from syphilis, acute gonorrhœal urethritis and epididymorchitis, and from cystitis, gonococci and *B. coli* being present in the urine. The patient was very ill indeed. I gave a dose of 25 millions autogenous *B. coli*, with the result that a severe rigor ensued. I at once told Mr. Pardoe that this was pathognomonic of pus under pressure. He made a most careful examination, but could find no focus of suppuration. Another similar dose a few days later produced the same effect. I expressed my conviction anew, and again Mr. Pardoe examined the case without result. I told him that none the less such a focus did exist. A few days later, while the doctor was introducing a catheter, just as the tip passed the anterior layer of the triangular ligament, two to three ounces of extremely foul bloody pus escaped, revealing the existence of an abscess as I

had predicted, but in a rare situation, viz. between the layers of the triangular ligament, where it could not be detected by manual palpation. After the evacuation of the pus the patient made a speedy and uncomplicated recovery. Doctors will be saved many mistakes, and escape the misapprehension which freely exists that vaccine of *B. coli* is highly toxic and appropriate initial dosages very low, if they will remember the above fact, that, especially in abdominal cases, if a dose of 25 millions *B. coli* vaccine produces a rigor, pus under pressure somewhere is certainly existent.

In acute urethritis, where the gonococcus is undoubtedly responsible for the condition, secondary infection by the other bacteria I have mentioned occurs after the first two to three weeks in a very considerable percentage of cases. If the case does well and speedily recovers from the gonococcal infection, the secondary invaders usually disappear with it. Occasionally they do not, and a condition of non-specific chronic urethritis is then engendered. When the gonococcal infection persists, the secondary invaders persist with it, and then a condition of chronic mixed specific and non-specific urethritis is set up. The wisdom of preventing secondary infection whenever possible is thus obvious, and this is best attained by keeping the penis well wrapped up in antiseptic gauze from the beginning, and by methodical irrigation with suitable antiseptics after the first ten to fourteen days. I am not going to enter into any discussion as to the value or wisdom of irrigation in the earlier stages. Mr. Wyndham Powell is opposed to the procedure, and the very considerable experience I acquired while in command of the Venereal Section of the New Zealand Expeditionary Force convinced me that he is right.

As to the correct procedure to be followed in the

vaccine treatment of acute gonococcal urethritis and the value of the method, a considerable diversity of views exists. I believe I was undoubtedly the first to practise vaccine treatment of acute cases. I began my researches with a perfectly open mind, tried every imaginable scheme of dosages, and soon convinced myself that the only dosage of any value is, as is invariably the case, that dosage which produces a definite focal reaction, and that the higher this dosage can be made without the evoking of any excessive degree of reaction, the better is the result. Initial doses of 2 to 5 millions may just as well be put down the sink; they entirely fail to produce an adequate response. Initial dosages of 10 millions in uncomplicated cases are also quite inadequate; but if the literature be searched, dozens of utterly unconvincing papers will be found, usually written by men quite devoid of clinical experience of gonorrhœa, who employed initial dosages of $\frac{1}{2}$, 1, $2\frac{1}{2}$, 5, and 10 millions, some claiming good results, some saying the treatment was a failure, but none stating that focal reactions were induced or giving a method of controlling dosage which by any stretch of the imagination can be called scientific. I have given very many hundreds of initial dosages of 50 millions in uncomplicated cases and of 25 and rarely 10 millions in complicated cases, and have never yet seen an undesirable reaction evoked nor a complication induced. When a complication exists, the appropriate initial dosage is the dosage appropriate to the complication, for instance in a mild prostatitis or epididymitis 25 millions, in a severe prostatitis or epididymorchitis 10 millions, as in the latter cases the local hyperæmia induced by the higher dosage may induce excessive pain and swelling for a day or two.

Subsequent dosages and intervals will depend entirely

upon the reactions produced, constitutional as well as focal in pyrexial cases, and will be further controlled by the general condition of the patient and the methodical examination of smears, not only for bacteria but also of the type of exudate cell contained therein. The presence of three and four lobed polymorphs, as opposed to one and two lobed, is a good sign, as is also their steady replacement by lymphoid and plasma cells. The plan which I found to answer best in the army was, as soon as possible after the admission of the patient and the completion of his examination, to give a dose of 50 millions in uncomplicated cases and of 10-25 millions in complicated cases, to give Pot. Cit. mixture in order to render the urine alkaline, reinoculate as soon as indications pointed to that course, begin thorough irrigation twice daily with weak permanganate of potash or cyanide of mercury on about the tenth day, and prostatic massage on about the seventeenth to twenty-first day. The dosage of vaccine was increased as rapidly as possible, owing to the exigencies of military service and the necessity of securing the highest possible degree of immunity in the shortest possible time. Despite the fact that I took over the treatment of many chronics, some of whom had had the disease for six months, the average stay in hospital of all my cases was reduced to twenty-three days by the end of six months. I compared results with Colonel Harrison at Rochester Row, and he agreed that my results were exceptionally good. The vaccine used in these cases was one compounded of 40 per cent. of sensitized bacilli and 60 per cent. of unsensitized, which had, however, been treated with normal serum and repeatedly washed with normal salt solution to render them atoxic; they were emulsified and sterilized in salt solution containing 1 part of HCl in 3,000,

which prevents autolysis and the liberation of their endotoxin. This vaccine I consider to be superior to the "detoxicated" vaccine of Capt. D. Thomson, wherein autolysis is promoted by the addition of weak caustic soda solution, the bacillary protoplasm being precipitated from the solution by the addition of acid, collected, dried, and then emulsified. Nearly four years ago I made trial of a few vaccines made on this principle, and certainly obtained some very good results with them. I, however, considered them faulty in conception, as by the complete removal of the endotoxin from the vaccine all stimulus to the formation of anti-endotoxin by the tissues is withdrawn. In some infections in which endotoxin is of little moment this may not matter much; but in others, wherein endotoxin plays a prominent part, this withdrawal of all stimulus to the formation of anti-endotoxin may well prove to be the determining factor in rendering the vaccine treatment of no avail. Thorough washing of the bacilli with salt solution will, in practically all instances, free them sufficiently from the endotoxin which has been liberated by the autolysis of some of their members, and from the products of their metabolism derived from the culture medium (see p. 30).

No case was discharged as cured until three films on successive days proved negative; if any doubt existed, the prostate was massaged and a dose of silver nitrate instilled into the posterior urethra at night, and a fresh smear taken in the morning. As by arrangement with the British authorities all cases of venereal disease in the New Zealand Army were sent to me and any relapse had to be immediately returned to me, I was able to keep a perfect check on all my cases.

Complicated cases were treated on similar lines,

vaccine treatment being continued until a final dosage of 500 to 1,000 millions failed to excite any focal or general reaction.

Cases of **orchitis** proved to be much the most obdurate and also the most liable to recur if sent back to training too soon ; for this reason they were always given one or two final doses of 1,000 millions. The initial dose should not exceed 25 millions.

In chronic cases the nature of the secondary infection was always carefully determined, but more attention was given to the extinction of the gonococcus than to freeing the patient entirely from the secondary invaders and from all traces of mucoid discharge. The number of patients was such as to make it impossible for me to employ secondary vaccines in all cases ; whenever I thought it really necessary this was done, otherwise the only vaccine used was the gonococcal one. While I am convinced on theoretical grounds and as the result of actual experience that the very best result can only be achieved by the use of mixed vaccines, I am not at all certain that the duration of the gonococcal infection is very materially reduced thereby ; where their influence is the more clearly seen is in the speed with which the mucoid non-gonococcal discharge or gleet is caused to disappear. Not that all cases of gleet can be so completely cured by the use of the appropriate autogenous mixed vaccines that no trace whatever of early morning discharge is to be found ; but this can be achieved in the great majority of cases when the appropriate surgical measures (dilatation, etc.) are also taken, and those cases in which this ideal result cannot be achieved can be safely assured that the specific infection is extinct when they fail to react both focally and constitutionally to 1,000 million doses of the vaccine.

I think it can be fairly claimed for the treatment of acute and chronic gonorrhœa by means of vaccines of the gonococcus and the secondary invaders, that (1) the course of the disease is favourably influenced and its duration materially shortened ; (2) complications are rendered less frequent ; (3) relapses are diminished ; (4) the danger of chronicity markedly reduced ; (5) a reliable test is afforded of the disappearance of the gonococcal infection and of the safety with which matrimony may be entered upon.

The appropriate initial dosages for the secondary invaders in chronic cases are staphylococcus 250 millions, *B. influenzæ* and *pseudo-influenzæ* 100 millions, diphtheroids, *B. coli*, *B. proteus*, *B. of Friedländer*, streptococcus, and pneumococcus 50 millions.

For subsequent dosages and intervals no rule of thumb can be laid down. The reactions and examination of smears afford all the requisite guidance, but as a rule seven to ten days' intervals are not far amiss.

Men of wide experience like Colonel Harrison of Rochester Row hold decided views of the utility of vaccines in gonorrhœa, and Mr. Wyndham Powell tells me that he is convinced that they possess a far greater potentiality for good than such methods as irrigation, ionization, local antiseptics, thermotherapy, etc., excluding of course such well-proved methods as methodical dilatation and the topical application of antiseptics to infected crypt and follicles with the help of the urethroscope.

Infections of the Genital Tract in Women.—Most of what has been said regarding the disease in man holds with equal truth where women are concerned. The disease is so much the more serious an affair for women, owing to the risk of endometritis and salpingitis which

are so little amenable to stereotyped methods of treatment, that it might well have been anticipated that vaccine treatment would have had a very full and fair trial. Strange to say, this has not been the case, and gynecologists have as a body studiously avoided vaccine treatment, apparently preferring always to wait until operation affords the only chance of restoration to comparative health. I know of no English gynecologist and of only one or two in America who have even given the most superficial trial to vaccines, except in a few cases of puerperal endometritis, and nowhere does a more fruitful field exist for study.

The bacteriology of the normal vagina is a very complex one, but in cases of infection a proper technique will remove all difficulties in arriving at a correct diagnosis of the infective organisms. The normal uterus above the cervix is sterile, so no difficulty whatever exists here in infective conditions. The tubes and ovary are of course inaccessible, but post-mortem results show that in acute conditions the only common infective agents are the gonococcus, *B. coli*, streptococcus, and staphylococcus, and the difficulties of deciding which of these is to be held to account are by no means insuperable.

The parts are so highly vascularized that the response to vaccine treatment should be exceptionally good; drainage from an infected uterus is by no means bad. Thus the greatest difficulty presenting itself in the vaccine treatment of these parts lies in the difficulty of observing the focal reactions. Constitutional symptoms, however, are as a rule a prominent feature, and the general reaction should afford a good and perhaps sufficient guide to the administration of the vaccine. Initial dosages may be taken as similar to those in cases

of septicæmia, for cases of acute endometritis, metritis, and salpingitis frequently pass into a condition of septicæmia ; and it may be here mentioned that blood cultures should always be made in these conditions. I have mentioned on p. 176 how this procedure would have prevented a serious blunder in a recent case of puerperal endometritis.

Disease of the Genital Tract in Children.—A considerable amount of study has been devoted to the vaccine treatment of vulvo-vaginitis in children in America, where the disease seems very prevalent. Butler and Long (*Journ. of Amer. Med. Assoc.*, 1908, p. 744, *ibid.* p. 1301), Hamilton and Cooke (*ibid.* 1910, p. 2123), Churchill and Soper (*ibid.* 1908, p. 1298) have all treated large series of cases due to gonococcal infection by means of vaccine and compared their results with those they obtained by other methods. They found that the vaccine treatment presented the most marked advantages over any other method, both with regard to the percentage of cures and the time taken to effect a cure.

The initial dosage in young children which apparently gives the best result is one of 5-10 millions. Hamilton and Cooke treated 84 cases with vaccines and 260 without. They cured 90 per cent. by the first method, only 60 per cent. by the others ; the average stay in hospital of the vaccine cases was 1.7 months, of the others 10.1 months.

The treatment of **tuberculous disease** of the genito-urinary tract differs in no way from the treatment of tuberculous disease of the respiratory system. The same necessity exists for taking into prior consideration the presence of any mixed infection, and for first getting this under control by means of the appropriate vaccines.

When this has been done, attention may be turned to the tubercle bacilli.

Dosages and intervals are determined in the usual way, as described under pulmonary tuberculosis (p. 173).

As an initial dose one may use .00001 c.c. of old tuberculin, albumose-free tuberculin, or of T.R., or .0001 c.c. of Martindale's tuberculin "M," preferably of mixed human and bovine types. Ultimate dosages of .001-.01 c.c. of the former varieties, and .01-.1 c.c. of the latter variety may have to be attained before cure can be considered to be complete; this, however, is a matter that can only be determined by the clinical progress of each individual case.

The infection is of a serious character, and, so far as one can judge, both vaccines and tuberculin materially increase the chances of recovery.

CHAPTER XIV

DISEASES OF THE EYE

Diseases of the—	Infective agents.
Lids	Staphylococcus, streptococcus
Conjunctiva	Gonococcus, pneumococcus, streptococcus, B. of Friedländer, B. coli, B. pyocyaneus, M. catarrhalis, Koch-Weeks bacilli, Morax-Axenfeld B., B. tuberculosis
Lachrymal sac	Streptococcus, pneumococcus, staphylococcus
Cornea and sclera	Gonococcus, pneumococcus, streptococcus, staphylococcus, B. coli, B. pyocyaneus, B. tuberculosis
Iris, ciliary body, retina, and choroid	Gonococcus, pneumococcus, streptococcus, staphylococcus, B. tuberculosis

I VENTURE to say that no part of the body gives such striking results in vaccine treatment of the diseases peculiar to it as the various parts of the eyeball. Vaccine treatment has quite special claims to recognition, for the following reasons :

- (1) Surgical methods have probably developed as far as they are capable of developing.
- (2) The extreme rapidity with which infective processes develop, the extreme gravity of the resultant damage if these are allowed to proceed unchecked, and the great likelihood of removal of the eyeball having to be adopted; whereas vaccine treatment is capable of dealing with quite 90 per cent. of these cases.

(3) The great liability to sympathetic involvement of the other eye.

(4) The excellent guidance as to dosage and interval afforded by the clinical observation of parts so accessible as these are.

(5) The excellent blood supply and consequent ready access to the parts, cornea and sclera excepted, offered to the antibodies.

It is now many years since I was the first to apply vaccine treatment to diseases of the eye. I had facilities and opportunity for the study available to very few, inasmuch as my colleagues at the Royal Eye Hospital placed all their cases unreservedly at my disposal. Of these opportunities I fully availed myself, and I venture to say that I left few microbic diseases of the eye unstudied. I approached the subject with an absolutely open mind, tried all sorts of dosages and all sorts of methods until I finally evolved more or less settled plans which yielded results that in 90 per cent. of the gravest cases left practically nothing to be desired. In my lectures and my various books I gave these freely to the profession, but, with the sole exception of a paper in the *Practitioner* in the very early days of vaccine treatment, omitted to publish any of my researches in a journal or periodical of wide circulation. Probably as a result of this, in no branch of medicine or surgery has vaccine treatment been so shamefully neglected. Very few papers on the subject have been published, and in the few that have been, the results recorded have been mediocre to fair, for the simple reason that none of these writers seem to have been aware of my thorough and systematic work, or to have profited by my warnings as to the absolute necessity of employing high dosages in these parts. One and all they have

used dosages which even in my early writings I condemned after full trial, as being utterly inadequate. Naturally I feel partly to blame for not having sought wider publicity for my work, but perhaps it is not yet too late for vaccine treatment to demand and receive its right place in the treatment of bacterial diseases of the eyeball. One thing I certainly can promise my readers: if only they will follow the advice and methods I give in this chapter they will achieve results that they now think outside the sphere of practical politics, and preserve to their unfortunate owners many an eye with sight practically unimpaired which otherwise will hardly fulfil the rôle of an imperfect ornament. If this is to be brought about it is necessary to remember:

(1) That some infections, such as those of gonococcal and pneumococcal hypopyon ulcers, progress at times with such rapidity to panophthalmitis that no time can possibly be lost; the diagnosis should be made from stained films and a dose of reliable stock vaccine at once administered. Without delay the preparation of the autogenous vaccine should be proceeded with, lest, the stock vaccine failing to suit the case, no appropriate vaccine be available for use the following day.

(2) That ocular diseases may only be secondary manifestations of primary foci elsewhere—for instance, gonococcal iridocyclitis of a primary urethritis, phlyctenules of a primary pulmonary or glandular tuberculosis. It thus follows that the doctor must not fix his attention solely upon the offending eye, but also direct it to all other parts of the body. An iridocyclitis may clear up with two or three doses of vaccine; not so the urethritis—so that when recurrence takes place, it is not another failure to vaccine treatment, but another

failure to the careless administrator who neglected to seek for the real cause of the trouble.

(3) That without an accurate diagnosis success is not to be achieved. Eye organisms are not only as a rule haemophyllic, but some require special media for their culture. No case has been properly worked out bacteriologically if blood agar and serum agar have not both been used in possible conjunction with other media. The Koch-Weeks bacillus only grows freely in presence of blood or serum, the Morax-Axenfeld bacillus freely only on solid blood serum. The outer parts of the eye are also very open to contamination with air-borne bacteria. The conjunctival spaces should always therefore, when time permits, be thoroughly flushed out with sterile salt solution, and the open eye lightly covered with a pad for an hour or two prior to taking of cultures.

(4) High dosages of all vaccines are especially appropriate to ocular infections. Probably owing to the small area of tissue involved in primary infections of the eyeball, toxæmic symptoms are rarely present ; the tissues of the body are therefore capable of elaborating the necessary antibodies with exceptional speed, and do so. In severe and dangerous infections this is all to the good of the patient, and I have never seen produced any of the chimerical effects of the "negative phase."

Control of Dosages and Intervals.—This throughout will be by means of the readily observed focal and general reactions. By means of the ophthalmoscope, the changes, even in the iris, choroid, and retina, can as a rule be closely watched, unless the cornea be marred by opacities or the anterior chamber be filled with pus. In these cases more superficial parts may afford the necessary guidance. Even high dosages like 500 millions

pneumococci or gonococci may be repeated at two to three days' intervals if clinical symptoms and focal reactions indicate the advisability. I have repeatedly done so, despite a natural hesitation, and nothing but good has resulted. At the same time never inoculate for the sake of inoculating or of doing something; you should always be able to render a good reason for the procedure if asked.

Diseases of the Lids.—The common diseases of the lids are stye, marginal blepharitis, and eczema. For these, staphylococci are usually responsible, sometimes associated with the acne bacillus; occasionally streptococci are responsible. The appropriate initial dosages are 250 millions staphylococcus, 5 millions acne bacillus, and 50 millions streptococci. As a rule ordinary treatment suffices without recourse to vaccine being necessary.

Diseases of the Conjunctiva.—The most common infections of the conjunctiva, *i.e.* those by the Koch-Weeks and Morax-Axenfeld bacillus, are readily cured as a rule by ordinary methods of treatment. I have, however, met with some most obstinate cases of chronic conjunctivitis, due to the Morax-Axenfeld bacillus, which would not respond at all to months of treatment with anti-septics and yet yielded to two or three doses of 250 millions of the vaccine at weekly intervals. Either 100 or 250 millions can be given as the initial dose. Conjunctivitis due to Friedländer's bacillus makes up for its rarity by its extreme obstinacy to ordinary methods. Vaccine is hardly likely ever to fail. Initial dosage, 100 millions.

Staphylococcal conjunctivitis is occasionally troublesome, but again vaccine will effect a cure. Initial dosage, 250 millions. A somewhat common form, affecting infants two to four weeks after birth, is sometimes very

refractory to antiseptics, but soon clears up with an autogenous vaccine. Initial dosage for this age, 50 millions.

When we come to conjunctivitis due to the gonococcus, pneumococcus, streptococcus, and *B. pyocyaneus*, especially when traumatic in origin, as they usually are, I think vaccine treatment should be little short of compulsory. The rapidity with which at times the conjunctivitis passes into hypopyon and panophthalmitis is such that once seen is never to be forgotten. A few doses of vaccine cost but little, and practically remove all possible danger. In these cases I think it is a sound rule to say the more acute and dangerous the infection, the larger the initial dosage. The minimum ever to use in these cases for an adult is 100 millions, and as a rule 250 millions will give a better result; the next dose may be required any time between the second and fifth days. For young children from half to one-fifth of the above dosage is advisable.

One case I had at the Royal Eye Hospital remains in my memory, and although it is only one of many, is worth quoting because it was seen by several others of the staff. The man walked into Professor McHardy's out-patients' department with double gonococcal conjunctivitis and complete hypopyon of one eye. He was so bad that I realized that vaccine alone could possibly save the sight of at least one of the eyes. I showed him to Mr. Vernon Cargill and Mr. Ormond, and they agreed that the prognosis was very grave indeed. I accordingly gave him at once 250 millions gonococcus vaccine. Just as I had done so Professor McHardy entered the room, agreed with the prognosis, and left the case to me. Although the patient was so careless of himself that he neglected to employ the lotion prescribed and to keep

guards upon the eyes, the discharge and chemosis had almost disappeared by the fourth day, when he was given the same dose of vaccine again. On the eighth day cure was practically complete. On the tenth day I showed him to Professor McHardy, who looked at the man and inquired why I was showing him, as he could see nothing the matter with him.

About the same time we had quite an epidemic of pneumococcal conjunctivitis among young children, which advanced so rapidly that hypopyon was common within twenty-four hours. In one case when I was taking a culture with the utmost care, perforation occurred and the lens was extruded. To all these cases I gave doses of 100 to 250 millions of pneumococcal vaccine, with the result that all got well, including the above case that perforated, with very little impairment of vision. In most cases the sight was normal.

Chronic conjunctivitis, due to the *B. tuberculosis*, varies considerably in clinical characteristics, and is almost invariably secondary to tuberculosis elsewhere. For this reason treatment has sometimes to be prolonged over a considerable period, especially in the nodular form, in order to bring about a cure. None the less I am convinced that the administration of mixed tuberculin, in initial dosages of .00001 c.c., has a definite influence in promoting cure.

Dosages and intervals require to be controlled by the clinical changes and reactions produced at the primary focus of infection, rather than by those resulting at the ocular focus, though these also have to be taken into account.

Diseases of the Lachrymal Sac.—The acute forms as a rule yield to ordinary treatment; in the chronic forms trial should always be made of an autogenous vaccine

before resorting to extirpation. Although chronic dacryocystitis is almost invariably a sequel of acute conjunctivitis, the bacteria responsible for the latter are usually supplanted by a streptococcus, sometimes by the pneumococcus or staphylococcus. To several cases due to the streptococcus which were doing badly under ordinary treatment, I have given vaccine in initial dosages of 100 millions. Cure has always been established in six to eight weeks by means of vaccine combined with the appropriate surgical measures.

Diseases of the Cornea and Sclera.—The ulcerative forms may be set up by a variety of organisms: interstitial keratitis, phlyctenular keratitis, and episcleritis are usually due either to the *B. tuberculosis* or *Treponema pallidum*, but secondary infections may be set up by other organisms. The treatment of the acute ulcerative forms is precisely similar to that of cases of acute conjunctivitis due to the same organisms. The same necessity exists for promptitude and adequate dosages. For details of several interesting cases the reader is referred to *Vaccine Therapy*, 4th edition, p. 311. .

In practically all the successful cases of vaccine treatment recorded in literature the dosages I have laid down have been administered. In nearly all the unsuccessful cases smaller, and usually much smaller, dosages have been given. This may help to impress upon the reader the prime necessity of administering full dosages.

An interesting form of chronic ulceration of the cornea is that known as "ulcus serpens corneæ." This I have found to be due in all the cases I have seen to the pneumococcus. Parsons and others have tried applications of antipneumococcic serum without success. I have never found vaccine to fail me in preventing any further progress of the disease, and in leading to some restitution

of the damaged parts. Ophthalmic surgeons find the disease so intractable, and the resultant damage to the vision is so serious, that the neglect of vaccine treatment is most regrettable. Initial dosages of 100 to 250 millions of the autogenous vaccine will be repeated or increased at intervals controlled by clinical observation. As a rule intervals of seven to ten days are not much amiss.

There is also a form of chronic ulcerative keratitis, resembling a condition common in Samoa, due to a member of the *M. catarrhalis* family. A general superficial erosion of the cornea progresses to an infiltration of the more superficial, then of the deeper layers of the cornea. The intra-ocular tension falls considerably and vision is gradually lost. The few cases I have seen have responded well to doses of 250 millions of the autogenous vaccine, progress of the disease being stayed, some repair of the parts and return of vision also occurring.

In the tuberculous forms the treatment is the same as in tuberculous conjunctivitis, prior attention being directed to any secondary invaders before attacking the *B. tuberculosis*. Phlyctenular keratitis progresses very slowly, and is apt to recur. Treatment has to be conducted, therefore, over a sufficiently long period, and if the primary focus fails to heal, short immunizing courses of five or six inoculations, with dosages approximating the highest ones attained in the therapeutic course, must be given twice yearly in order to diminish the liability to relapse.

Diseases of the Iris and Ciliary Body, Retina and Choroid.—Tuberculous forms are treated on the lines laid down for tuberculous conjunctivitis, and quite satisfactory results are usually obtained. Treatment, how-

ever, should not be given up prematurely, but must be continued for several weeks or months after apparently complete cure has resulted in order to prevent relapse.

The gonococcal and pneumococcal varieties are treated on the lines already given on p. 277, but the almost certain existence of a primary focus elsewhere must never be lost sight of, especially in the gonococcal form, and until the urethritis has been completely cured the patient is always in danger of a relapse. Cases associated with gonococcal arthritis are apt to prove refractory, and exacerbations and relapses in the two conditions usually occur together. As no case of gonococcal arthritis can be considered to be cured until it fails entirely to react focally or generally to doses of at least 1,000 millions of vaccine, this dosage should always be attained in cases of gonococcal iritis or iridocyclitis before vaccine treatment is suspended.

Two conditions, especially interesting in view of the difficulties they present, are rheumatic iritis and toxic choroiditis. Rheumatic iritis is the name given by ophthalmic surgeons to all cases of iritis of unknown origin. Occasionally it may be associated with the *Streptococcus rheumaticus*; much more commonly it is associated with the streptococci and other bacteria responsible for the condition of advanced pyorrhœa usually found in these cases. Sometimes, too, the *Streptococcus faecalis* and coliform bacilli of a stagnant colon, cæcum, appendix, or sigmoid are concerned in its ætiology. The correct treatment is therefore entirely dependent upon a right understanding of its ætiology. If pyorrhœa be responsible, careful dental treatment and a vaccine of the mouth streptococcus, or other microbes setting up the pyorrhœa, will usually materially influence the iritis. If intestinal stagnation be the

cause, this must be remedied, and perhaps a vaccine of the intestinal organisms will be of assistance. The vaccine treatment of the iritis is thus resolved into the vaccine treatment of the condition responsible for the iritis. What I have said regarding the iritis holds with equal force for the choroiditis.

CHAPTER XV

DISEASES OF THE DUCTLESS GLANDS

THE only disease of the ductless glands in which vaccine treatment has as yet found an application is **goitre**. Major McCarrison (*The Thyroid Gland in Health and Disease*) in fifteen years of laborious and careful research has conclusively shown that endemic goitre is due to the drinking of water contaminated with the faeces of goitrous individuals. He is of opinion that there is a specific organism capable of producing goitre which exists in man living in districts where goitre is endemic. He has not yet succeeded in isolating this specific germ, and so has not been able to prepare vaccines of it. He has, however, prepared mixed autogenous vaccines of such intestinal organisms as the staphylococcus, streptococcus, *B. coli*, and also a spore-bearing organism from a goitrous horse, and claims to have produced good results by giving these in increasing doses of 150 to 1,000 organisms at weekly intervals. A staphylococcus vaccine alone has also done good, and he explains the action of these various vaccines by assuming that they aid the disappearance of organisms which are secondary invaders to the primary specific undiscovered microbe.

I must confess that I fail to understand why McCarrison should presuppose the existence of a specific microbe. If, as he states, the cause lies in a bacterial toxin which stimulates the gland to increased activity,

it is hardly reasonable to suppose that one toxin alone possesses this faculty, especially in view of the fact that he has experimentally produced the disease in rats and goats by feeding them on faecal material derived from goitrous and non-goitrous subjects alike.

CHAPTER XVI

QUESTIONS AND ANSWERS

(1) *Q.*—My patient was doing quite well for a time, then ceased to improve. I increased the dosage, but instead of getting better, he has if anything got worse. What should I do?

A.—The first thing to do is to reinvestigate the bacteriology. An infection by an organism either completely absent before or present only in very small numbers is quite possibly at the root of the trouble. If, however, this proves not to be the case, give your patient at least a month's rest, then begin treatment again with half that dosage which he was receiving when he ceased to improve and increase slowly.

(2) *Q.*—I have under my care an infant two years old; he has just developed broncho-pneumonia. I do not like the prospect. I have had the sputum examined, and only pneumococci are to be found. Do you advise vaccine treatment, and how should I proceed?

A.—See Chapter VIII, p. 164. A good deal depends upon the degree of toxicity apparently present. In any case the information that pneumococci alone are present is not of much value, if there is immediate danger. The information wanted is what type of pneumococcus (see p. 160). If this is not known, it should at once be ascertained. If you have antipneumococcal serum of the corresponding type, I advise you to give 20 c.c. intravenously at once, and 10 c.c. more six to ten

hours later, continuing its use daily thereafter in quantities dependent on the resultant change in clinical condition. Meanwhile I should advise the preparation of a sensitized vaccine with a view to its administration at once in an initial dose of 10 millions if the right serum is not available; if, on the other hand, the serum has been used and the patient (a) has not improved, it will probably be no use giving vaccine; (b) has definitely benefited from its use, begin with the vaccine as soon as the patient has turned the corner; it will probably expedite recovery and prevent undesirable sequelæ.

(3) Q.—Mr. X., for whom you made an autogenous vaccine for his bronchitis, is going away for a month, and fears he will not be within reach of a doctor, and wants to take two or three doses with him for self-administration. Shall I consent to this?

A.—This is a very delicate question, and much depends on the nature and character of Mr. X.; with this you should be well acquainted. Self-administration is not a success, even with doctors, if they have to depend on their own judgment in deciding dosage. But if you can absolutely depend upon Mr. X. and upon his carrying out your instructions, and you particularly do not wish any interruption of the treatment, you may accede to the request. Instruct him minutely in the technique, impress upon him the dangers of sepsis and the necessity of sterilizing everything; put up for him the necessary doses in ampoules, not making any increase in the dosage; extend the intervals by two to three days, giving him all the directions in writing. See that he has a reliable syringe and needles which may be kept in a bottle of absolute alcohol, **but absolutely disclaim all responsibility in writing, and keep a copy of the letter.**

(4) Q.—I was taught that the *Bacillus proteus* is *non-*

pathogenic, and the only books on bacteriology that I have state so. I have had repeated examinations made of the urine in a case of cystitis, and this microbe is found invariably present in large numbers and in a state of purity. Is it to be regarded as being the cause of the cystitis, and would it be worth while trying a vaccine, as other usual methods of treatment have failed?

A.—Before being able to give a definite answer, I should like to know (1) whether the urine has been centrifugalized and direct smears made and carefully examined for other bacteria, including *B. tuberculosis*—it is easy to miss a few streptococci or *B. tuberculosis* amid a large number of other microbes, especially if these multiply rapidly at room temperature; (2) what cultural media and methods have been adopted for the isolation of the infective agent. In the event of the answers to these questions being satisfactory, and excluding the possibility of another infective agent being present, the fact that the *Bacillus proteus* is commonly regarded as being non-pathogenic presents no obstacle to your acceptance of this organism as the true infective agent.

The description of any bacillus as being *non-pathogenic* is a survival of the day of rigid adherence to Koch's postulates, which have done more to impede progress in bacteriology as applied to medicine than any other factor. Every day it becomes increasingly clearer that microbes which so far entirely fail to satisfy these postulates (and in my opinion always will fail to satisfy them) are by no means destitute of pathogenic properties in man, and accordingly give rise to various symptoms. For instance, it has recently been shown that such a common air organism as *B. subtilis*, previously regarded as being perfectly harmless, can be caused

to exhibit a definite pathogenic action. I long ago decided to discard the application of Koch's postulates to practical medicine; their fulfilment finishes off a piece of experimental work, especially upon diseases of unknown origin, very nicely, but their non-fulfilment is no justification for excluding any microbe from the rôle of being the causation of any pathological condition and for withholding the possible advantages to be derived by any sufferer from a course of vaccine treatment. Furthermore, recent experience has shown conclusively that non-pathogenic organisms like *B. proteus* and *M. tetragenus* can under suitable conditions assume pathogenic properties and give rise to serious symptoms. You need therefore have no hesitation in making use of a vaccine of the organism in question, especially as experience has shown that cases of cystitis frequently do exceedingly well under vaccine treatment.

(5) *Q.*—Doubt is being cast on the view that the *B. influenzæ* is really ever the true causation of so-called influenza: if these doubts are justified, is it any use giving a vaccine of it for prophylactic purposes?

A.—Here again we have theory running contrary to practical experience. Some bacteriologists of high repute are even now questioning whether Ebert's bacillus is the real cause of typhoid fever, or only a secondary invader. This is the heyday of the filterable viruses, which are enjoying a popularity equalled only by that of Lloyd George, Clemenceau, and President Wilson, and quite possibly with equal justification.

None the less, the only test of real value is that of practical experience, and few remain who question the good effect produced by prophylactic treatment with antityphoid vaccine. It is a fact that the *B. influenzæ* is very rarely indeed seen in pure culture from the secre-

tions, and only seldom obtained from the blood. I in thousands of cases have never seen it in absolute purity in the sputum, the nearest approach to it being in very chronic cases, but there is no doubt that many of the symptoms of influenza are due to the presence of these organisms of questionable repute, and that by judicious immunization their presence can be obviated or determined. Practical experience shows that thereby the patient is freed of most of his distressing symptoms and that the mortality rate in epidemics of the inoculated is very much lower than that of the uninoculated. At the same time pay due attention to the fact that the pneumococcus, streptococcus, and *M. catarrhalis* are commonly, if not invariably, associated with it, and if you wish to immunize your patient to the best advantage, you must employ a mixed vaccine, such as my combined vaccine for colds.

(6) *Q.*—I have been treating a patient on ordinary medical lines with distinct advantage, but cannot cure him, and propose to make trial of a vaccine. Shall I discontinue my present procedure while doing so?

A.—On no account, unless you can think of other measures likely to be of greater assistance to the vaccine: the therapeutic use of vaccine is never meant to displace other remedies, and the clinical experience of centuries is not to be discarded lightly, even in the case of purely empirical remedies. The two treatments seldom clash in any way, and are usually of mutual assistance.

(7) *Q.*—Are there any definite contra-indications to vaccine treatment, and if so what are they?

A.—See p. 78. This question is of much greater importance than formerly, owing to the greatly increased number of nephritics, the result of trench fever and

other diseases of warfare, and of those suffering from disordered action of the heart. All bacterial toxins are mainly excreted through the kidneys, and the administration of a vaccine leads to the production of considerable quantities of toxin derived not only from the bacilli in the vaccine, but from those killed at the foci of infection as the result of the vaccine. It thus follows that the tubules of the kidneys, already seriously damaged by the trench fever, may be unable to excrete the bacterial toxins as rapidly as they form, with the result that the cells receive further damage from which they may be slow to recover, and as a result thereof albumen may again be excreted in the urine for a few days, and other symptoms of trench fever reappear. In a few cases apparently fresh attacks of the fever have been thus originated. The accumulation of toxins in the blood is also not without effect in the cases of disordered action of the heart, especially when these are primarily toxic in origin ; the musculature of the heart is possibly more susceptible to bacterial toxins than any other tissue of the body. While the history of trench fever or D.A.H. is no absolute contra-indication to vaccine treatment, it is in my opinion a reason for exercising special care in selecting the initial dosage, and I think a rule should be made in these cases of reducing the usual initial dosage to one-half or even one-third ; if no ill-effects manifest themselves after the first two or three dosages, it is quite easy then to push the dosage in the usual manner.

(8) *Q.*—I never hear the opsonic index mentioned now ; is it altogether a dead letter, or is it of any real value in vaccine treatment ?

A.—Very few workers now ever employ it in treatment, holding, as I do, that the reactions, clinical signs and symptoms, coupled with clinical experience in the

use of vaccines, afford sufficient assistance. At the same time it is of very material assistance (*a*) in experimental work in determining the dosages which give rise to the speediest and highest formation of antibodies, and in estimating how best these can be spaced ; (*b*) in diagnosis, where, especially in cases of apparently mixed infection, it is often of the very greatest value in sorting out the agent really responsible for the condition. Such a good example is afforded of this in a case reported by Byers and Houston (*Lancet*, June 1913, p. 1723) that I give full details.

A boy of ten years had for eight years suffered from obscure catarrhal attacks : on this occasion one began as usual, but suddenly spread to the ear and chest ; broncho-pneumonia of both lungs and pleura ensued, and the temperature shot up to 105° . Swabs from the throat, nose, and sputum at first showed streptococcus, *M. catarrhalis*, and a few Gram-positive diplococci ; later a pure culture of the *M. tetragenus* was obtained from these sites, and a day or two later from the blood and urine. The temperature was $102-104^{\circ}$, there was severe diarrhoea and steady emaciation.

Three microbes at least were thus the possible cause of the trouble, and of these the *M. tetragenus* is seldom considered to be pathogenic. The opsonic index being raised only to this organism ($1.7-2.1$), an autogenous vaccine of it was given in doses of $2\frac{1}{2}-4$ millions, with the result that the temperature became normal on the fifteenth day of treatment, and an uninterrupted recovery was made.

(9) *Q.* I have heard much of the dangers of anaphylactic shock in serum treatment. Is any similar danger to be feared with a vaccine ? If so, how can I obviate it ?

A. Theoretically, there is a danger ; practically, none

exists. In fifteen years, with the exception of one case, the most serious effect produced within three hours of the administration of a vaccine has been fainting of seven patients, but inasmuch as this occurred *immediately* after the administration, or rather began during it, the phenomenon cannot have been due to anaphylaxis, which never comes on prior to the lapse of a few minutes, but must have been central in origin, and probably purely psychic in nature. On one occasion, however, I have seen a very severe and nearly fatal attack of acute pulmonary oedema result from the injection of a large dose of vaccine. Both the time of onset and nature of the symptoms closely corresponded to those due to anaphylaxis, and although I did not see the case until two to three hours after the onset, I am persuaded that the attack was really due to anaphylaxis. This, however, is the only case of the kind that I have seen, or of which I have heard. If, however, fear of anaphylaxis is really present in your mind with regard to any particular case, you can easily avoid all danger by giving a minute dose, say 1 to 5 millions, first, and the remainder of the dose one to three hours later.

(10) *Q.*—My patient is steadily improving under the scheme of dosages you advised, but he never appears to have a reaction. Is this all right, or what shall I do?

A.—What possible better reaction could you have or desire than steady improvement? Some of my very best results, both therapeutic and prophylactic, have been in those who have given no signs whatever of local or general reactions other than steady improvement. These, for some reason which I cannot explain, have always been people distinctly on the fat side, and they have made no more response to very large doses than to small ones. Leave well alone and carry on.

(ii) *Q.*—What is the final dosage you recommend of your combined vaccine for colds for prophylactic purposes, and can any kind of general rule be laid down?

A.—For people who react constitutionally strongly to this vaccine, the 500-millions dose is probably as high as you and they will care to go, but if this be so the dose should be repeated at least once, and if possible two or three times. For other people who do not react so strongly, the 1,000-million dosage repeated once is desirable. Three points are to be remembered: (a) that the resultant immunity is decided within limits and with certain reservations by the total several amounts of vaccine given; (b) that all the little experimental evidence available points strongly to the conclusion that a few large doses at intervals of seven to ten days are less toxic, but incite the formation of a greater degree of immunity than a larger number of small doses at short intervals, which in sum-total correspond to the few large doses; (c) evidence yielded by the same set of observations indicates that when a certain dosage is reached the maximal immunizing response is attained, and the administration of larger doses, or even of more doses of the same dimensions, may only lead to a diminution in the amount of antibodies present in the serum. For this reason I feel that it is unwise ever to conduct too protracted a course of treatment, and that after a certain time, even if the patient is not cured, it is better to stop treatment for a while, give the tissues a rest, and begin again with half the highest dosage previously attained.

As regards the possibility of laying down any rule, this can hardly be done for all microbes, as some are so much more toxic than others. At the same time some rough working rule can be given as follows. A total

dosage of 4,000 to 5,000 millions of *B. typhosus* has been found experimentally and clinically to incite good immunity for at least six months. Take this as a basis. From the table given on p. 35 of the number of bacteria corresponding to 1 milligram of direct bacterial substance, calculate the numbers of the microbe in question which correspond to 4,000 to 5,000 millions of the *B. typhosus*, and take the result as the total dosage to be given. Personally I cannot agree with some of the figures given. For instance, if 1 mgm. of dried *B. typhosus* contains 8,000 millions, I feel that 1 mgm. of dried streptococci should contain more like 12,000 millions than the 3,400 millions there given. This is borne out by the results of Hopkins (*Journ. Amer. Med. Assoc.*, 1913, vol. xl. p. 1615), who, like myself, standardizes his vaccines by thorough centrifugalization and the dilution of the precipitated microbes to form a 1 per cent. emulsion. His figures closely correspond to my own in many cases, viz. that for a 1 per cent. emulsion 1 c.c. contains in thousands of millions: staphylococci, 10; streptococci, 8; gonococci, 8; *B. typhosus*, 8; *B. coli*, 4; and pneumococcus, 2.5. With the last two I disagree and give *B. coli* 6, pneumococci 10, this last being a very serious difference—the accuracy of my figure being rendered much the more likely by the practical observations of Lister and the Rockefeller Institute. On this basis if we require a total of 4,000 millions *B. typhosus* to give good immunity, we require a total of 5,000 millions pneumococci, 5,000 millions staphylococci, 4,000 millions streptococci, 3,000 millions *B. coli*, and so on—numbers which correspond well with the figures indicated by clinical experience, which is perhaps our best guide.

(12) Q.—I have a patient going to Egypt for a long

holiday, who wishes to be vaccinated and to be inoculated against typhoid and cholera. Can this be all done at the same time, and will you do it, and will any alterations in dosage have to be made?

A.—There is no objection whatever to vaccinating one arm and giving the combined antityphoid-anti-cholera vaccine in the other at the same time, and no reduction of dosage is necessary.

There was considerable urgency about the case, so I vaccinated the right arm and gave 1,000 millions of antiseptic sterilized vaccines of each of *V. cholerae*, *B. typhosus*, *B. paratyphosus* A and B in the left arm. Although I vaccinated in four places it only "took" to a very slight degree indeed. No marked reaction, local or constitutional, occurred as regards the vaccine, so a week later I gave the 2,000-millions dosages again without any ill effect. The young lady went to Cairo and escaped all infection, although it was a very bad season from the health point of view. Six months later the agglutination titre of her serum was as follows: To *B. typhosus*, 1 in 80; to *B. paratyphosus* A, 1 in 50; to *B. paratyphosus* B, 1 in 100.

(13) *Q.*—I have a patient shortly going to China, who wishes to be protected against plague, cholera, and typhoid. Can this be done satisfactorily at the same time?

A.—See p. 75. While the answer is in the affirmative, it must be remembered that antiplague vaccine often causes a considerable degree of local and constitutional reaction, and that this is true to a less degree with regard to the others. The patient should therefore be warned to expect this. The general health should be good, and the patient should abstain for two or three days from all alcoholic drinks, and should have only a

light lunch and dinner. Let him go to bed about nine o'clock and inoculate him afterwards. He should be supervised during the night and be in a position to receive proper attention if required.

If the temperature rise unduly, remove superfluous bed covering and sponge with cold water; if a rigor ensue, apply hot-water bottles. If the arm become unduly tender and painful, first put on a hot compress; if this does not give relief, apply crushed ice and evaporating lotions. For the ensuing twenty-four hours the diet should remain quite light. If no ill-effects ensue from the first inoculation, they are not to be apprehended from the second or third, nevertheless the same precautions should be taken.

(14) *Q.*—I have heard so many contrary opinions given about stock vaccines that I should much like to hear yours. My especial concern is regarding a case of gonorrhœal arthritis and chronic gleet.

A.—A general answer can hardly be given to the question, so many factors are involved. Rarely, for instance, will you have any idea of the age of a stock vaccine; makers would be wise, as with sera and as is compulsory in Australia, to indicate the date at which the vaccine should be discarded. While I am certain that some vaccines, as those of streptococci in general and *Streptococcus rheumaticus* in particular, even improve with age up to a certain limit, and are perfectly good after three years, others, such as antityphoid vaccine, especially if heat-sterilized, begin to deteriorate after twelve months, even when stored in a cool dark place, and guarantee is usually lacking that the vaccine has been kept by the seller under proper conditions. Again, a stock vaccine should be compounded of many strains, say at least ten. Of these it may be that only

one or two are capable of inciting the formation of the antibodies appropriate to the case ; it thus follows that the actual dosage administered is only one-tenth or one-fifth of that indicated by the maker and desired to be given by the user.

Thirdly, if a stock vaccine is to be employed, only those made by men who, besides being competent bacteriologists, are also experienced clinicians, should be bought. Personally I never incorporate in any stock vaccine strains which have not given a good clinical result in the case for which it was made. Some strains of bacteria of low pathogenicity have high powers of exciting immunity ; for instance, the *B. typhosus* used to make the antityphoid vaccine of the American Army is stated to be totally devoid of pathogenicity, but capable of exciting the production of very large amounts of immune bodies. The converse is equally true. I have isolated strains of pneumococcus and streptococcus of extraordinary virulence, but of very little use as vaccines. So-called clinical laboratories are therefore by no means to be relied upon as manufacturers of good stock vaccines, lacking as they do opportunity for observing the effects of their autogenous vaccine. In the reliance they may consequently place, if they are extra-conscientious people, upon animal experimentation, I am not much of a believer, as I have often known strains of bacteria of extreme virulence to men reported upon as even being non-pathogenic, because they have failed in a given time to kill mouse or rabbit. There is only one test of the value of a vaccine, and that is the results achieved with it in man.

Admitted that one is in possession of a thoroughly reliable stock vaccine, and a case of urgency arises, you should not hesitate to employ that stock vaccine

at once, and take steps to have an autogenous one made. The time thus saved may mean the life of the patient. Sometimes the preparation of the autogenous vaccine may present unusual difficulties, as for instance in the case you mention. Gonococci may be undoubtedly present in the urethra, but be so outnumbered by secondary invaders that the isolation of the gonococcus may be almost an impossibility. Or again, even when the infection is almost a pure one, the microbe may either refuse to grow on cultural media or under artificial conditions, as especially in the case of the *B. influenzæ*, or, if it does grow, may prove to be devoid of adequate immunizing power. In such cases a well-tested stock vaccine obviously possesses a definite advantage over the autogenous one. In your case, therefore, I think you will be well advised to give trial first to a reliable stock vaccine, adjusting your dosage to begin with, with an eye to the urethral condition rather than to the arthritic. It may also be necessary to incorporate with the gonococcal vaccine one directed against the secondary infection in the urethra, and for this an autogenous vaccine is almost certain to be necessary.

(15) *Q.*—I have a case of acute generalized infection where I suspect the pneumococcus or streptococcus. Is a vaccine likely to be of any use?

A.—This depends. In no class of case have I had such conspicuous success as in that of septicæmia; in fact, I have never yet had a failure.

There is, however, one question which is of outstanding importance, *i.e.* is the generalized infection due to a focal infection with which it is possible for a surgeon to deal or not? If it is, and the patient has any resisting power left, speedy operation and prompt administration of the vaccine should make success assured; but if it is

not accessible, then vaccine treatment is hardly likely to be of much service.

(16) *Q.*—I have had for some time under my care a boy now aged sixteen. At the age of twelve he had a protracted attack of whooping cough, but without complications. Ever since he has had a bad cough, his tonsils are enlarged, and so are some of the glands in his neck. He is very tall (6 ft. 1 in.), and has overgrown his strength, and his mother is much concerned about the question of consumption. For some months I have been inoculating him with a vaccine of *B. influenzæ*, *pneumococcus*, and *M. catarrhalis*, made from his sputum. He improved for some time, but then ceased to do so, although I increased his dosage to 250 millions of each. What do you advise me to do?

A.—I replied, I cannot possibly advise without seeing the boy. Having had other cases of the kind, I suspected that he might be a case of chronic whooping cough. The boy was duly brought by his mother, and I was able to reassure her concerning the question of pulmonary tuberculosis. There was very little the matter with the lungs at all, but the tonsils were very much enlarged, and were affected with follicular tonsillitis, the uvula was swollen and œdematosus, and there was some chronic granular pharyngitis. The post-nasal and naso-pharyngeal spaces contained much mucus, slightly tinged with yellow. Having defined opinions concerning the possible diagnosis, I had several plates of glycerine potato blood agar ready, took swabs from the tonsils and posterior pharyngeal wall, and made several cultures upon plates. On examining these at the end of twenty-four hours there was abundant growth of *B. influenzæ*, *pneumococcus*, *streptococcus*, and *M. catarrhalis*, and a few pin-point colonies very like small ones of *B. influenzæ*.

Some of the plates were returned to the incubator. Next day the *B. influenzae* colonies were more numerous and larger, but there were in addition more pin-point colonies than before, and those seen at the end of twenty-four hours had increased in size and were more heaped up and whiter than those of *B. influenzae*. Next day they were still larger, definitely larger than those of *B. influenzae*, more heaped up, with rounded surfaces, and less translucent. These were unmistakably colonies of Bordet's bacillus. Next day they were characteristic of that bacillus, and double to treble the size of the *B. influenzae* colonies. A vaccine was now made of the five organisms found, and treatment begun with doses containing 100 millions *B. influenzae* and Bordet's bacillus, and 50 millions of the other three. The dose was repeated in five days. Five days later 250 millions of the first two and 100 millions of the other three were given, repeated twice at seven-days' intervals, by which time the cough was practically gone. After two doses of double the above strength it had gone completely, and no Bordet's bacillus could be seen or cultured. The cure was a permanent one.

Now this case was a very lucky one. Any bacteriologist might be pardoned for thinking that after he had examined smears thoroughly, made cultures on blood agar, and apparently succeeded in culturing all the microbes seen, that the case was worked out thoroughly. I was, however, on my guard, because I had seen two or three other similar cases, the first one of which had had an identical history. In this I was struck by an apparent difference in the *B. influenzae* colonies at the end of thirty hours' incubation, and investigated some of them more closely, finding out that I was dealing with two different microbes. When it is recalled that

B. influenzae and pneumococcus occur along with Bordet's bacillus in 90 per cent. of the cases of acute whooping cough, the possibility of the infection by *B. Bordet* persisting should be always borne in mind.

I venture to predict that chronic infection by Bordet's bacillus will be found to be quite a common occurrence, and feel it is constantly missed owing to the association with the *B. influenzae* of identical morphology. Many of the aberrant types of *B. influenzae* described by bacteriologists are really Bordet's bacillus.

(17) I will conclude with a question I received from a doctor in the North of Ireland, who wrote: "I quite understand your description of how to inoculate, *i.e.* pick up a good fold of skin between finger and thumb, and plunge the needle boldly in, but what do I do when I have pushed it right through the opposite side?" The answer I felt inclined to give was, "Keep on pushing," or something in the strain of, I think it was Lord Rayleigh, to whom an old lady at the close of a lecture to which she had listened with rapt attention remarked: "Dear Professor, I have enjoyed the lecture so, and understand everything except that you did not make clear the difference between oxygen and hydrogen." The Professor replied, "My dear lady, very little; the one is pure gin, the other gin and water."

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